“METABOLIC EVALUATION IN PEDIATRIC RENAL STONE FORMERS”

Dissertation submitted for

M.D. DEGREE EXAMINATION

BRANCH VII- PAEDIATRIC MEDICINE

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INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

CHENNAI

CERTIFICATE

This is to certify that the dissertation titled **"Metabolic Evaluation In Pediatric Renal Stone Formers"** at **Institute of child health and hospital for children** submitted by **Dr. M.NIVETHA,** to the Faculty of Pediatrics, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Pediatrics) during the academic year 2012 – 2015 is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I solemnly declare that this dissertation entitled **"Metabolic Evaluation In Pediatric Renal Stone Formers" at Institute of child health and hospital for children** was done by me at Madras Medical College and Institute of child health, during 2012-2015 under the guidance and supervision of **Prof. R.Padmarajan M.D., D.C.H., D.M.** This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in Pediatrics (Branch-VII).

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr. Nivetha .M,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Metabolic Evaluation in Renal Stone forming children"** No.33042014

The following members of Ethics Committee were present in the meeting held on 08.04.2014 conducted at Madras Medical College, Chennai-3.

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8.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

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The incidence of urolithiasis in children is very much in the
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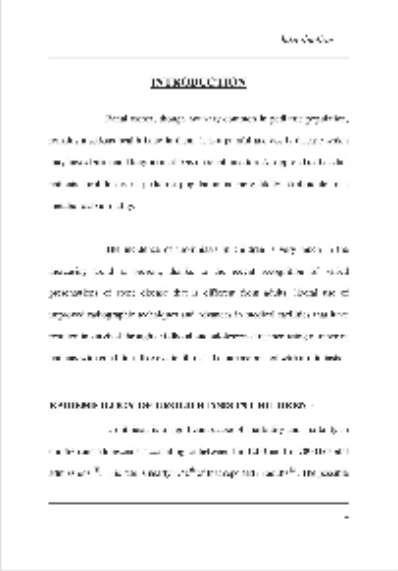

INTRODUCTION

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METABOLIC EVALUATION IN PEDIATRIC RENAL STONE FORMERS

ABSTRACT

BACKGROUND:

Renal stones, though not very common in pediatric population, remains a serious health issue in them. Metabolic causes can be found in majority of children with urolithiasis. By identifying the exact cause, we would be able to prevent recurrences and the development of end stage renal disease. Thus the aim of the study is to identify metabolic factors leading on to stone disease by analyzing the 24 hour urinary metabolic parameters.

METHODOLOGY:

50 children with urolithiasis are subjected to metabolic evaluation involving renal function test, serum uric acid, vitamin D, parathyroid hormone, calcium, phosphorus, alkaline phosphatase, urine pH, urine routine, urine culture, urine sodium nitroprusside test, 24 hour urine calcium, oxalate, citrate and uric acid. arterial blood gas analysis is done for children with suspicion of distal renal tubular acidosis.

RESULTS :

Out of the 50 children with urolithiasis, hyperoxaluria was present in 26 children (12- isolated and 14- mixed abnormalities). Hypercalciuria was present in 16 children(4 - isolated and 12- mixed). No metabolic abnormality could be identified in just 3 children. Distal RTA was diagnosed in 2 children who had nephrocalcinosis with normal anion gap metabolic acidosis with high urine pH. None of the patients had cystine/ struvite stones.

CONCLUSION:

24 hour urine metabolic workup is the gold standard in metabolic evaluation of patients with urolithiasis. Hyperoxaluria followed by Hypercalciuria and Hyperuricosuria were the most common metabolic abnormalities detected in our patients. Thus early detection and treatment of metabolic abnormality must be stressed upon to prevent recurrences and development of end stage renal disease.

INTRODUCTION

Renal stones, though not very common in pediatric population, remains a serious health issue in them. It is a painful and costly disease which may have detrimental long-term effects on renal function. As opposed to the adult patients, urolithiasis in pediatric population is more likely attributable to a metabolic abnormality.

The incidence of urolithiasis in children is very much in the increasing trend at present, thanks to the recent recognition of varied presentations of stone disease that is different from adults, liberal use of improved radiographic techniques and advances in medical facilities that have resulted in survival through childhood and adolescence of increasing number of patients with conditions like cystic fibrosis that are associated with urolithiasis.

EPIDEMIOLOGY OF UROLITHIASIS IN CHILDREN :

Urolithiasis is a significant cause of morbidity and mortality in children and adolescents, accounting for 1 in 1000 to 1 in

7800 hospital admissions [1]. This rate is nearly 1/50th of that reported in adults [2]. The possible reason for the lesser incidence of urolithiasis in children is due to the presence in the children of very high concentrations of urinary inhibitors like citrate, magnesium and other macromolecules when compared to adults [3]

Similar to adults, children and adolescents with urolithiasis also tend to show an increased male preponderance [4,5] , but the male to female ratio is 1.4-2.1:1 in children, in contrast to 3:1 in adults. Regional variations in dietary intake, climatic conditions, fluid intake and genetic factors are known to influence the prevalence of renal stones, thus stressing the need for regional studies to identify the most commonly prevalent abnormality in one's own population.

ANATOMIC LOCATION OF THE STONE :

About 60 - 80% of urinary tract calculi in children are present in the kidneys at the time of diagnosis. The majority of the stones found in ureter, bladder and urethra have also originated in the kidneys. The bladder appears to be the site of stone formation in less than 10% in North America.

In India, endemic bladder stones are found, where the

bladder calculi are more often seen. A diet rich in whole–grain cereals, animal proteins, phosphates, oxalate rich vegetables with low calcium diet is believed to be responsible. [6,7] The resulting urinary profile favors precipitation of calcium oxalate, and ammonium acid urate, the most frequently encountered constituents of endemic bladder stones.

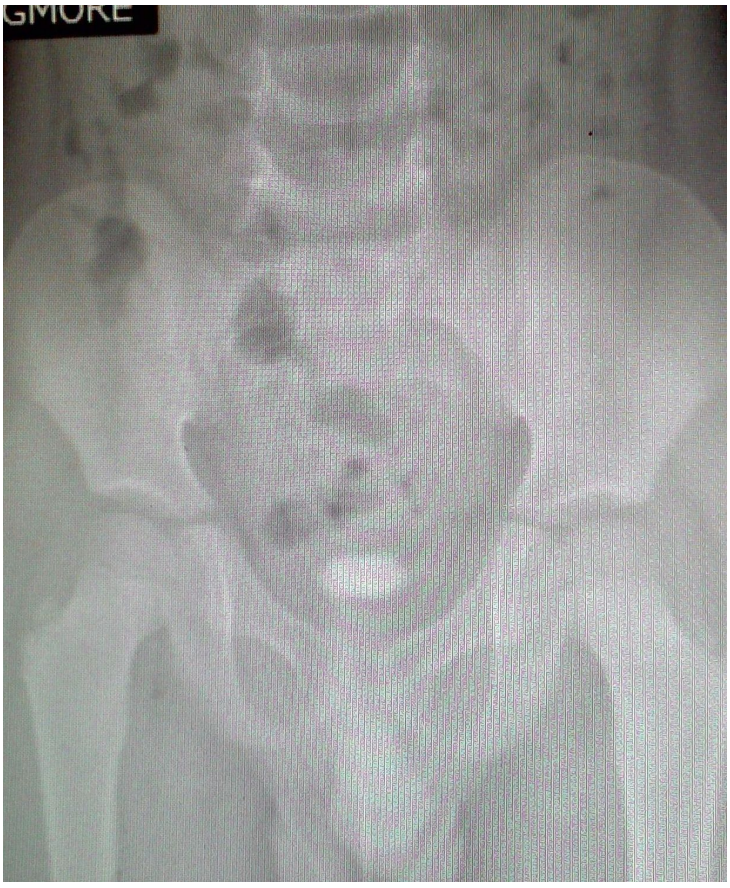


FIG 1 : Plain Xray of a 6 year old boy showing vesical calculus

PATHOGENESIS OF UROLITHIASIS :

Urinary stones develop usually as a result of the breakdown of a delicate balance between solubility and precipitation of solutes. The kidneys should conserve water, but they must also excrete materials that have a low solubility. It is these two opposing requirements that must be balanced during adaptation to diet, activity and climate. The problem is mitigated to some extent by the presence of some substances that inhibit crystallization in urine. These protective mechanisms are not very perfect. So, when the urine becomes supersaturated with insoluble substances, because excretion rates are high and/or because water conservation is extreme, crystals may form, grow and aggregate to form a calculus.

SUPERSATURATION :

A solution which is in equilibrium with crystals of calcium oxalate is said to be saturated with regard to calcium oxalate. If calcium oxalate crystals are removed, and if either calcium or oxalate ions are added to the solution, it will be found that the chemical activities increase, but no new crystals form. Such a solution is said to be

'*metastably supersaturated*'. If now, calcium oxalate crystals are added, the crystals will grow in size. Ultimately, as calcium or oxalate is added to the solution, supersaturation reaches a critical value at which a solid phase begins to develop spontaneously. This value is called the '*upper limit of metastability*'. On average, kidney stone growth requires urine that is supersaturated. Excessive supersaturation is commonly found in stone formers.

Calcium, phosphate and oxalate form many soluble complexes among themselves and with other substances in urine like citrate. Because of this, their free ion activities are well below their chemical concentrations. Reduction in substances like citrate can increase supersaturation by increasing the ion activity.

Urine supersaturation can be increased by

- Decreased urine volume
- Increased excretion of calcium, oxalate, phosphate, cystine, or uric acid.
- Decreased level of inhibitors like citrate, Magnesium, osteopontin etc.

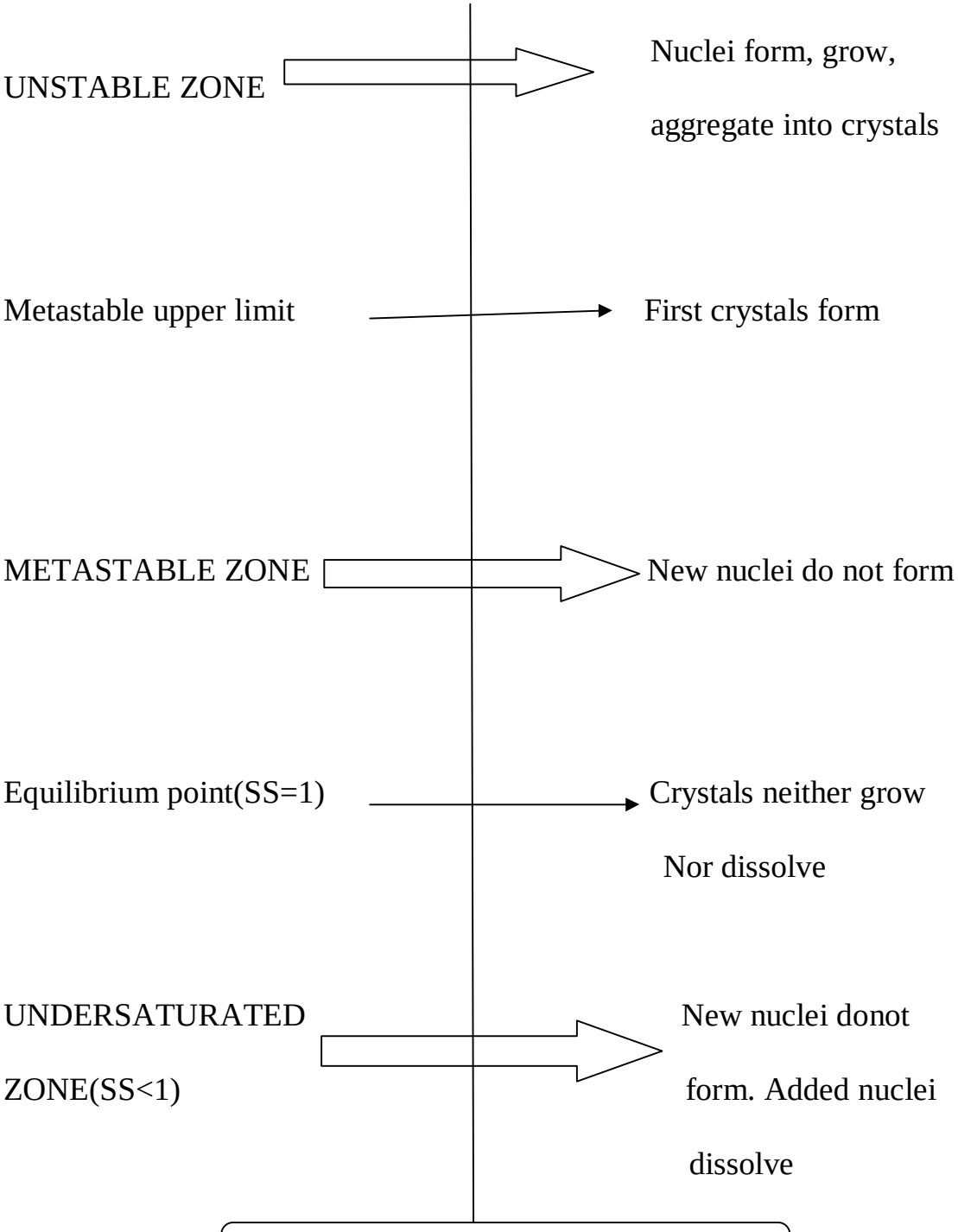


Fig 2 : Supersaturation (SS) of urine

Urine pH is also an important determinant of stone formation. Acids like phosphate and uric acid dissociate readily over the physiologic range of urine pH. Below a urine pH of 5.5, uric acid crystals are predominantly seen whereas phosphate crystals are rare. Alkaline urine contains more dibasic phosphate which favour the deposition of brushite ($CaHPO_4H_2O$) and apatite ($Ca_5(PO_4)_3OH$). Urine pH has no influence over the solubility of calcium oxalate

FIG 3: MAJOR URINARY ABNORMALITIES ASSOCIATED WITH STONE

Type Of Stone Former	pH	Component
Cystine	Acid	Cystine excess
Uric acid	Acid	Relative uric acid excess
Calcium phosphate	Alkaline	Relative calcium excess
Calcium oxalate Idiopathic Hyperoxaluric	pH range of normal urine	Calcium and oxalate excess Oxalate excess
Renal tubular acidosis	Alkaline	Calcium and phosphate excess
Magnesium ammonium Phosphate	Very alkaline	Relative magnesium, ammonium and phosphate excess

CRYSTALLIZATION :

When urinary supersaturation exceeds the upper limit of metastability, nucleation of crystals begin. Cell debris present in the urinary tract serve as templates for crystal formation. This process is known as *heterogeneous nucleation*. Heterogeneous nucleation reduces the level of supersaturation that is required for crystal formation. Once formed, crystal nuclei tend to grow in size if urine is supersaturated with that crystal phase. Following this aggregation of multiple crystals occur to form a stone.

For a kidney stone to develop, crystals must first be retained in the renal pelvis for a sufficiently long time for it to grow and aggregate to a significant size. The mechanism of crystal retention is always a matter of much debate. It is shown in recent studies that common calcium oxalate kidney stones form as overgrowths on the apatite stones (sub-epithelial plaques of calcium phosphate) in the renal papillae. These plaques, called Randall's plaques, establish an excellent surface for nucleation of calcium oxalate salts. [9]These plaques arise first in the deep medulla in the basement membrane of the thin limb of Henle’s loop and then spread to the basement membrane of the papillary

urothelium. In case the urothelium becomes damaged, the plaque is exposed to the supersaturated urine, and crystallization and stone formation occurs.

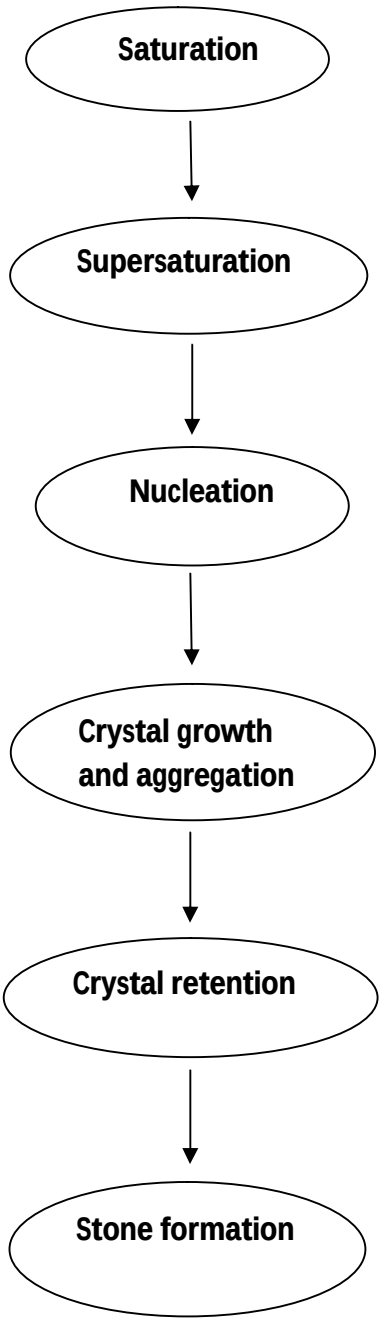


Fig 4 : Progression of lithogenesis

INHIBITORS OF CRYSTAL FORMATION :

Urine contains very potent inhibitors of nucleation, growth, adhesion and aggregation for calcium salts. Inorganic pyrophosphate is a potent inhibitor that inhibits formation of apatite crystals more than calcium oxalate crystals. Citrate though inhibits the crystal growth and nucleation, most of its stone inhibitory activity is due to lowering of urine supersaturation through complexation of calcium.

CLINICAL PRESENTATION OF URINARY TRACT CALCULI:

Symptoms of renal colic and hematuria, characteristic of urolithiasis in adults, are less often seen in children. Abdominal pain or hematuria are the most common presenting features in children with renal stones. In infants and toddlers, non specific abdominal pain is commoner than a typical renal colic. Indeed, in nearly half of the patients below the age of 5 years, the diagnosis of renal stones is made following a urinary tract infection or as an incidental finding during evaluation of other problems. [4]

STONE COMPOSITION :

Compared to adults, pediatric renal stone formers are more often associated with metabolic abnormalities. The common causes of renal stones in adults include calcium stones (75- 85%), uric acid stones (5-10%), struvite (5-10%), cystine stones (1%). Out of the calcium stones, 50-55% is due to idiopathic hypercalciuria, 20% is due to hyperuricosuria, 3-5% due to primary hyperparathyroidism, 10-30% due to hyperoxaluria (mainly dietary), idiopathic 20%.

In children, the various stones formed in upper urinary tract are as follows.

- Calcium stones - 70-85 %
- Struvite stones - 10-20%
- Cystine - 2-4 %
- Uric acid - 2-8%

CALCIUM STONES :

Calcium stones contain calcium oxalate or calcium phosphate or calcium oxalate and uric acid, or calcium oxalate and phosphate as constituents. The different causes for calcium stones include

- Hypercalciuria
- Hyperoxaluria
- Hyperuricosuria
- Primary hyperparathyroidism
- Distal renal tubular acidosis.

HYPERCALCIURIA:

Hypercalciuria, as defined as the urinary calcium excretion of > 4mg/kg/day, is a common cause of renal stones in children. Physiologic hypercalciuria is related to the dietary excess of sodium, protein, or calcium or to the deficiencies of potassium or phosphorus.

Most hypercalciuria is idiopathic. The mechanism implicated in idiopathic hypercalciuria include the following .

- Renal tubular phosphate leak
- Increased 1,25 dihydroxy vitamin D synthesis
- Increased renal prostaglandin E2 production
- Enhanced bone resorption.[10,11]

If hypercalciuria is detected, the patient must be placed in the proper category of causation of hypercalciuria. Four major causes exist.

TYPES FOR HYPERCALCIURIA :

TERM	PRESUMED CAUSE
Intestinal hyperabsorption	Excessive intestinal absorption of calcium
Renal leak	Failure of kidney to reabsorb tubular calcium
Bone resorption	Excessive calcium mobilised from bone
Carbohydrate load	Form of renal leak

GENERAL ASPECTS OF SEPARATION OF HYPERCALCIURIAS

TYPE OF HYPERCALCIURIA	S.Calcium	Urine Cyclic AMP	S. PTH	Fasting Urine Calcium	Bone Density	Intestinal Absorption
Primary hyperparathyroidism (bone resorption)	↑	↑	↑	↑	low	↑
Renal stones, absorptive	N	N or low	N or low	N	N	↑
Renal stones, "renal leak"	N	↑	↑	↑	?	N
Renal stones, normocalciuric	N	N	N	N	N	N

CAUSES OF HYPERCALCIURIA :

NORMOCALCEMIC HYPERCALCIURIA	• Idiopathic hypercalciuria • Distal renal tubular acidosis • Diuretic induced • Dent disease • Barter syndrome • Familial hypomagnesemia and hypercalciuria syndrome
HYPERCALCEMIC HYPERCALCIURIA	• Primary hyperparathyroidism • Immobilisation • Cushing syndrome • Adrenal insufficiency • Metastatic bone disease
INTESTINAL ABSORPTION OF CALCIUM	• Hypervitaminosis D or A • Sarcoidosis • Idiopathic hypercalcemia of childhood

GENETIC CAUSES OF HYPERCALCIURIA :

PROXIMAL TUBULE :

Dent's disease

Hereditary hypophosphatemic rickets with hypercalciuria,

Lowe syndrome)

THICK ASCENDING LOOP OF HENLE :

Bartter syndrome

Activating mutations of the calcium sensing receptor gene

Familial hypomagnesemia with hypercalciuria,

Nephrocalcinosis due to claudin 16 gene mutation

DISTAL TUBULE :

Pseudohypoaldosteronism type II

Primary renal distal renal tubular acidosis

Secondary forms of hypercalciuria may occur due to intake of drugs like furosemide or carbonic anhydrase inhibitors, or due to prolonged immobilisation, or high intake of calcium or vitamin D, or high concentrations of circulating PTH. Hypercalcemia of any cause may result in hypercalciuria.

HYPEROXALURIA :

Hyperoxaluria may be inherited or acquired.

PRIMARY	• Type I • Type II
SECONDARY	• Malabsorption syndromes like cystic fibrosis, inflammatory bowel disease, short bowel syndrome • Lack of intestinal oxalate degrading bacteria[13,14]

Primary hyperoxaluria is an autosomal recessive disorder caused due to the inborn error of glycine metabolism. It is of two types-type 1 and type 2.

TYPE I PRIMARY HYPEROXALURIA :

Type 1 primary hyperoxaluria is an autosomal recessive disease caused due to the mutations of the AGXT gene. This type

accounts for majority of children with primary hyperoxaluria. This is due to the deficiency of alanine glyoxylate aminotransferase, an enzyme which is expressed only in liver and it requires pyridoxine as its cofactor.

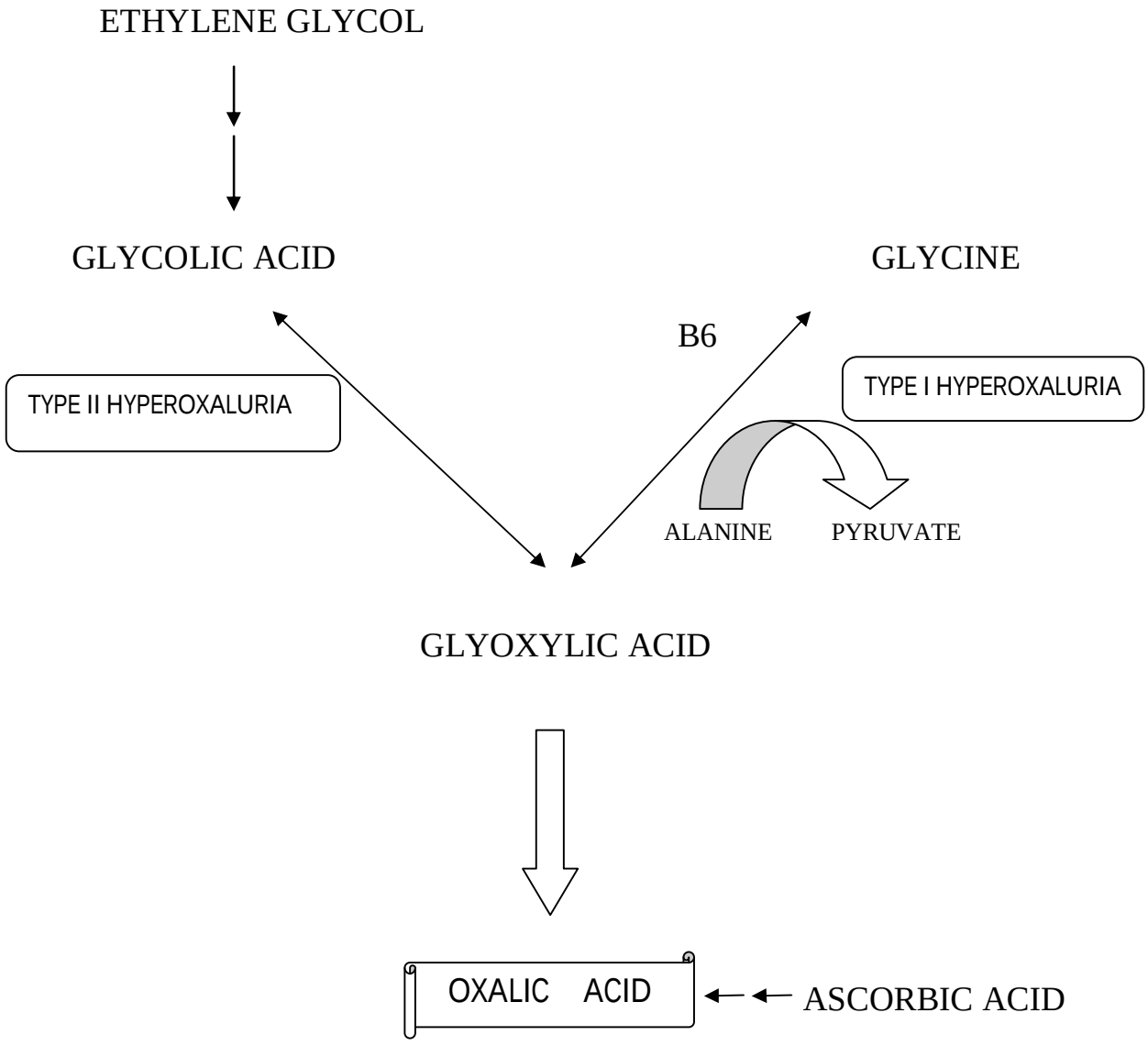


FIG 6: Metabolic pathway affected in primary hyperoxaluria

In the absence of this enzyme, conversion of glyoxylic acid to glycine cannot occur and it gets transferred to the cytosol and get oxidized to oxalic acid. Renal failure is common in children with type I primary hyperoxaluria.

DIAGNOSIS :

1. Marked hyperoxaluria
2. ↑ Urinary excretion of glyoxylic acid & glycolic acid
3. Enzyme assay in liver specimens
4. Mutant gene identification.

TYPE II PRIMARY HYPEROXALURIA :

Type 2 primary hyperoxaluria is due to deficiency of cytosolic enzyme glyoxylate reductase/hydroxyl pyruvate reductase. As a result of the deficient enzyme activity, the level of L-glyceric acid and oxalic acid increase and they are thus eliminated by the kidney. Renal failure is less in this condition.

DIAGNOSIS :

1. Marked hyperoxaluria
2. ↑ urine L-glyceric acid (with normal urine glycolic and glyoxylic acid levels)
3. Enzyme assay in liver specimens
4. Mutant gene identification

ENTERIC HYPEROXALURIA:

Enteric hyperoxaluria is the condition resulting from increased absorption of oxalate from intestine. Fat malabsorption and thus the conditions causing it, can result in hyperabsorption of oxalate from intestine. The reason behind this is the binding of calcium with the fatty acids in the intestine, thereby resulting in less calcium availability in the lumen for oxalate to which in turn gets absorbed readily.

OXALOBACTER FORMIGENES AND OXALATE STONES :

Recently, it has been identified that the degradation of fecal oxalate by some anaerobic bacteria that colonise the colon occurs

in a significant proportion of healthy population . The loss of such bacteria, like Oxalobacter formigenes is attributed to the increased absorption of oxalate from the gut and thus the formation of oxalate stones.[15]

HYPOCITRATURIA :

There are some naturally occurring inhibitors of stone formation. They are as follows.

1. Citrate
2. Pyrophosphate
3. Magnesium
4. Urinary macromolecules
    - Glycosaminoglycans
    - Osteopontin
    - urinary prothrombin fragments

Deficiency of citrate may be idiopathic or due to drug intake. In distal RTA, hypocitraturia is the main contributor for stone formation.

CYSTINE STONES :

Cystine stones are due to an inherited error of defective transport of cystine, and dibasic aminoacid such as lysine, ornithine, and arginine across intestinal and renal tubular cell membranes. Characteristic hexagonal shaped crystals can be seen in urine of patients with cystinuria. It is of two types - type I and type II.

TYPE I CYSTINURIA :

In type I cystinuria, the mutation is in the SLC3A1 gene on chromosome 2 and the urinary excretion of cystine is normal in heterozygotes[18,19]. It is inherited as autosomal recessive trait.

TYPE II CYSTINURIA :

In type 2 cystinuria, the mutation is in SLC7A9 gene on chromosome 19 , where the urinary excretion of cystine is moderately elevated in heterozygotes and much higher in homozygotes[20]. It is inherited as a dominant trait with incomplete penetrance.

Urine sodium nitroprusside test, a sensitive screening test for cystinuria is done in all patients with urolithiasis. Cystine stones are radio-opaque stones of intermediate density in radiographic imaging. If

cystine stones (characteristic hexagonal shaped cystine crystals) are positive in stone analysis or if the family history of cystinuria is present, then urine amino acid chromatography can be done to confirm the diagnosis of cystinuria.

STRUVITE STONES :

Struvite stone or infection stone occurs following infection with urease producing organisms, which split urea with resultant production of ammonium and bicarbonate ions. By this way the ph rises and in alkaline ph, phosphate dissociation occurs, resulting in the supersaturation of urine magnesium ammonium phosphate and calcium phosphate apatites.[21]

Struvite stones tend to form the staghorn calculus that grow rapidly and are difficult to treat. Uric acid stones are relatively uncommon in children.

$$NH_2CONH_2(\text{urea}) + H_2O \xrightarrow{\text{BACTERIAL UREASE}} 2(NH_3) + H_2CO_3$$

$$2NH_3 + H_2O \longrightarrow NH_4^+ + OH^-$$

(FIG 7: Production of ammonium by the action of bacterial urease on urea.because of excess of NH_4 ,the urine remains alkaline even if the renal excretion of acid is normal)

FIG 8 : Factors in the formation of magnesium ammonium phosphate calculi related to persistent alkaline urine.

Xanthogranulomatous pyelonephritis is a serious infectious condition affecting leading to non function of affected kidney[22]. A kidney damaged by calculi may be the site of replacement lipomatosis (xanthogranulomatous pyelonephritis). Organisms causing xanthogranulomatous pyelonephritis include the list below.[23]

- Proteus
- Klebsiella
- Staphylococcus

- Pseudomonas
- Enterobacter
- Ureaplasma urealyticum
- Providentia

In xanthogranulomatous pyelonephritis, infection, obstruction, and urolithiasis form a vicious cycle and complicate each other.

URATE STONES :

Hyperuricosuria may be primary or secondary. Idiopathic renal hyperuricosuria is often familial and asymptomatic. Mild idiopathic hperuricosuria may cause hematuria in some individuals[24]. Secondary hyperuricosuria may be a result of

- High protein diet
- High ketogenic diet
- Medications like ascorbic acid, dicumarol, probenicid, salicylates, citrate

Studies have documented the presence of secondary hyperuricosuria in patients with diabetes mellitus type 1 [25].

Hypouricemia and hyperuricosuria have also been reported to occur in patients with syndrome of inappropriate anti diuretic hormone secretion[26].

Uric acid stones, as such, are uncommon in childhood. When they are found in children, it is almost always due to the marked overproduction of uric acid in any one of the conditions listed below.

- Lymphoproliferative disorders
- Tumor lysis syndrome
- Inborn Errors of Metabolism - Lesch Nyhan syndrome (due to deficiency of hypoxanthine guanine phosphoribosyl transferase)
- Glycogen storage disease (Von Gierke's, Forbe-Cori's, Mc Ardle , Tauri disease)

XANTHINE CALCULI :

Xanthine calculi may be found in patients treated with allopurinol for hyperuricemia caused due to tumor lysis syndrome or Lesch Nyhan syndrome[27]. They are also seen in patients with autosomal recessive deficiency of xanthine oxidase or in patients with hereditary xanthinuria

OTHER SOLUTE EXCESS :

Rare inborn errors of metabolism causing urolithiasis include orotic aciduria, alkaptonuria ,adenine phosphoribosyl transferase deficiency[28,29}

CLINICAL CONDITIONS ASSOCIATED WITH UROLITHIASIS:

UROLITHIASIS AND RENAL TUBULAR ACIDOSIS :

DISTAL RTA:

Impaired acidification of urine, leading on to calcium stones, due to the reduced solubility of calcium in alkaline medium as well as metabolic acidosis, is the case in distal renal tubular acidosis.

Distal RTA results in hypercalciuria, hypocitraturia,low titratable acidity and high urine pH. Nephrocalcinosis due to calcium phosphate and /or calcium oxalate stones are characteristic and is seen with both complete and incomplete types of distal RTA[30].

Ammonium chloride loading test is useful in cases of incomplete forms to confirm the diagnosis of distal renal tubular acidosis. Failure of the urine to acidify even in the presence of acid load is diagnostic.

Secondary distal RTA due to Wilson's disease, Sjogren's Syndrome, type I GSD, cerebrotendinous xanthomatosis are also associated with urolithiasis.

PROXIMAL RTA:

Despite the occurrence of hypercalciuria in proximal renal tubular acidosis, urolithiasis is not usually found in these patients. It is attributed to the presence of high amount of citrate that may protect against stone formation[31]

TYPE IV RTA :

Urolithiasis is not usually associated with type IV RTA also. It is because the reduced excretion of calcium appears sufficient to compensate for the reduced citrate excretion, so that the urinary saturation of calcium oxalate remains within normal limits. Low uric acid and phosphorus excretion in these patients appear to mitigate against stone formation[32].

OBESITY AND METABOLIC SYNDROME :

Insulin resistance results in impaired renal ammonia production. Owing to the low urine ph, uric acid stone formation occurs[33]. In addition, the bariatric procedures performed during the treatment of obesity are associated with hyperoxaluria.

STRUCTURAL ABNORMALITIES OF URINARY TRACT:

- Medullary sponge kidney [34]
- Thin basement membrane nephropathy
- Posterior urethral valves
- Horse shoe kidney
- Ureterocele
- Primary megaureter
- Bladder extrophy- epispadius complex
- Autosomal dominant polycystic kidney disease [35]

PREMATURITY :

Preterm babies have higher incidence of nephrolithiasis and nephrocalcinosis when compared to healthy term babies. The following preterm babies are at high risk.[36]

- Extremely low birth weight babies.
- Those receiving furosemide
- Those receiving postnatal corticosteroids
- Longer duration of mechanical ventilation
- Parenteral nutrition
- Family history of nephrolithiasis

INFLAMMATORY BOWEL DISEASE :

Inflammatory bowel disease, and other diseases with associated malabsorption, can lead to hypocitraturia and hypomagnesuria due to the loss of bicarbonate and magnesium in stools. They also cause increased absorption of oxalate leading on to formation of oxalate stones. Due to increased cell turn over, hyperuricosuria may occur. Diarrhoea leading to dehydration and low urine volume may perpetuate stone formation[37].

DRUGS AND UROLITHIASIS :

Renal excretion of some medications may exceed its solubility limit in urine, or may induce some metabolic changes which may result in stone formation. The following are some of the medications associated with urinary calculi formation.

- Indinavir (common, 2-28%) [38]
- Ceftriaxone
- Sulfonamides
- Amoxycillin
- Triamterene
- Ampicillin
- Guafenesin
- Phenazopyridine
- Calcium, vitamin D supplements
- Cyclosporine
- Lithium
- Orlistat

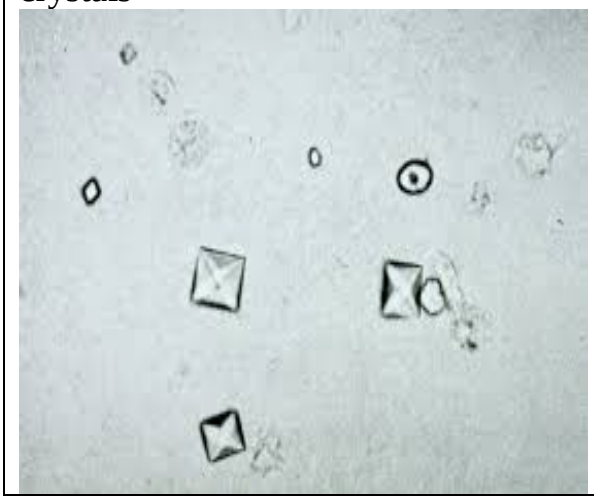
DIET AND UROLITHIASIS :

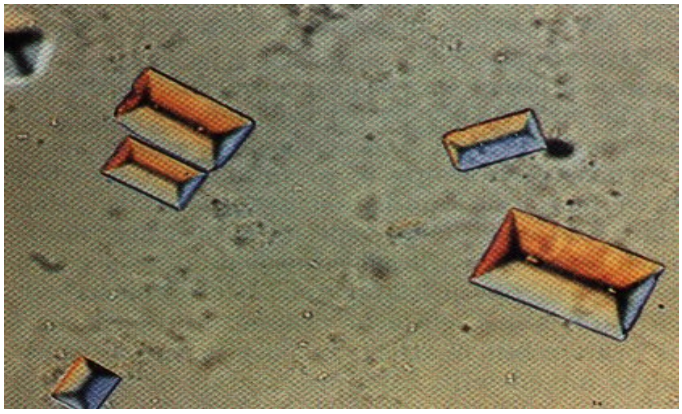
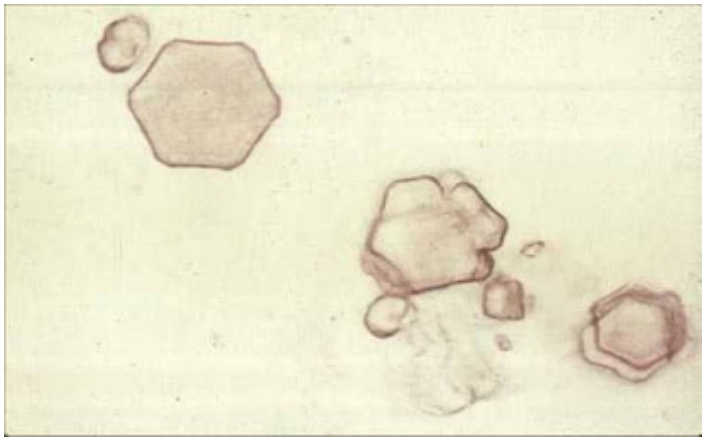
- High animal protein intake predisposes to the higher urine excretion of uric acid, calcium, and oxalate and reduced excretion of urinary citrate and reduced urine ph. All of these favour calcium oxalate stone stone formation.

- Intake of diet low in animal proteins but high in cereals lead to formation of endemic bladder stones in children.
- Large intake of sodium or calcium may result in hypercalciuria.
- High dietary oxalate, particularly if taken along with low calcium diet can lead on to hyperoxaluria.
- Fructose intake has been associated with hyperuricosuria, hyperoxaluria, insulin resistance and low urine ph, and thus the risk of stone disease.
- Contemporary weight loss diets like Atkins diet, which is rich in animal proteins but low in carbohydrates are associated with urolithiasis.[39]
- Ketogenic diet used for the management of refractory epilepsy is associated with nephrolithiasis.

CRYSTALS IN URINE MICROSCOPY:

Microscopic examination of the spun urine can be done to assess for RBCs and urinary crystals. Different crystals have different shapes in microscopy.

Calcium oxalate monohydrate crystals 	Spindle / oval / dumbbell shaped/ flat elongated "FENCE PICKET" crystals
calcium oxalate dihydrate crystals 	Colourless squares with intersecting lines (ENVELOPE like)

Triple phosphate (struvite) crystals 	Colorless, prism- like "COFFIN LIDS"
Uric acid crystals 	Yellow – brown rhombic plates / needles/ rosettes
Cystine crystals 	HEXAGONAL – shaped

IMAGING IN NEPHROLITHIASIS:

PLAIN X-RAY:

Most calculi are radio opaque and will be visible on plain x-ray (kidney, ureter, bladder [KUB]). But it should be understood that not all radio opaque shadows are stones and also that not all stones are radio opaque. A stone can be missed in case of bowel distension.

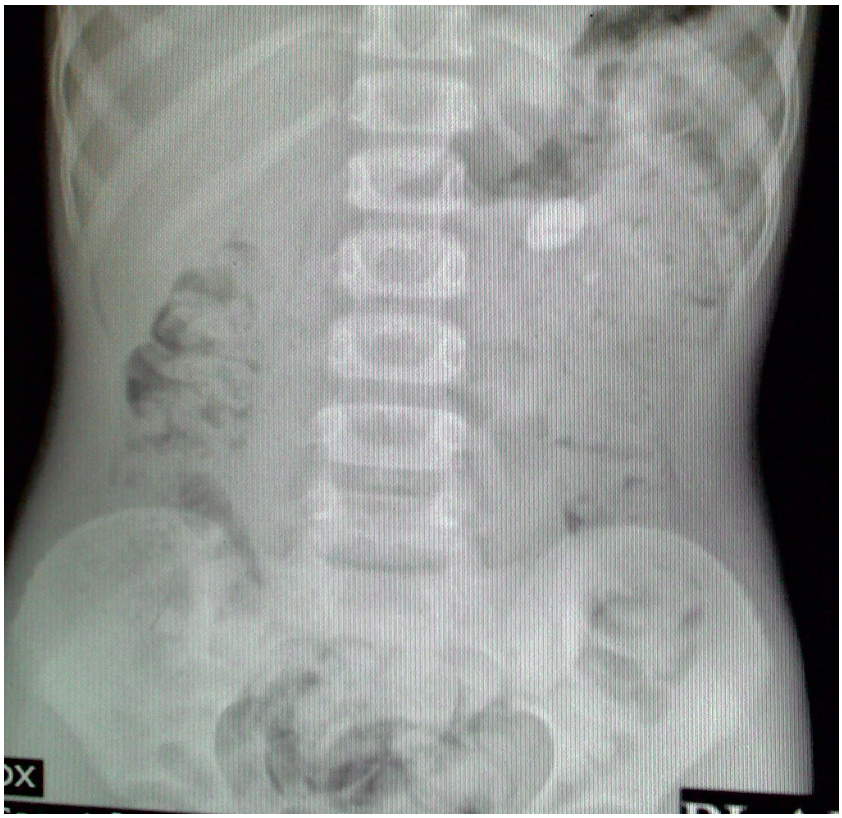


FIG 9: Plain Xray showing left side renal calculus in a 8 year old boy

ULTRASONOGRAPHY:

Ultrasound is another method for non invasive exploration of the child with urolithiasis. Ureteral calculi cannot be detected by ultrasonography except for that at proximal or distal ureters. However most ureteral calculi are either proximal or distal.

FIG 10 : Ultrasonogram showing right medullary nephrocalcinosis

ADVANTAGES:

1. Wide availability
2. Avoidance of ionising radiation
3. Ready detection of hydronephrosis
4. Detection of anatomical abnormalities

DISADVANTAGES :

1. Ultrasound is a good initial choice and in uncomplicated cases, it may be all that is needed. It is also the optimal imaging method for detecting and monitoring resolution of nephrocalcinosis.

2. Not as sensitive as CT scanning in small stone detection and for detecting stones in ureter .

3. Stone size measurement is less reproducible.

ULTRASOUND VERSUS KUB :

Ultrasound is found to be more sensitive than KUB in diagnosing a stone (84% versus 54%). However KUB is found to be more sensitive for ureteral calculi. A combination of KUB and urinary tract

ultrasound together allow an accurate diagnosis of around 90% of urinary calculi.

INTRAVENOUS PYELOGRAPHY :

Intra venous pyelography is the study of choice for the very rare calculi seen not seen on KUB film or ultrasound, especially ureteral calculi. IVP provides morphologic and functional information.

CT SCANNING :

CT scan is probably the most sensitive way to detect urinary tract calculi.

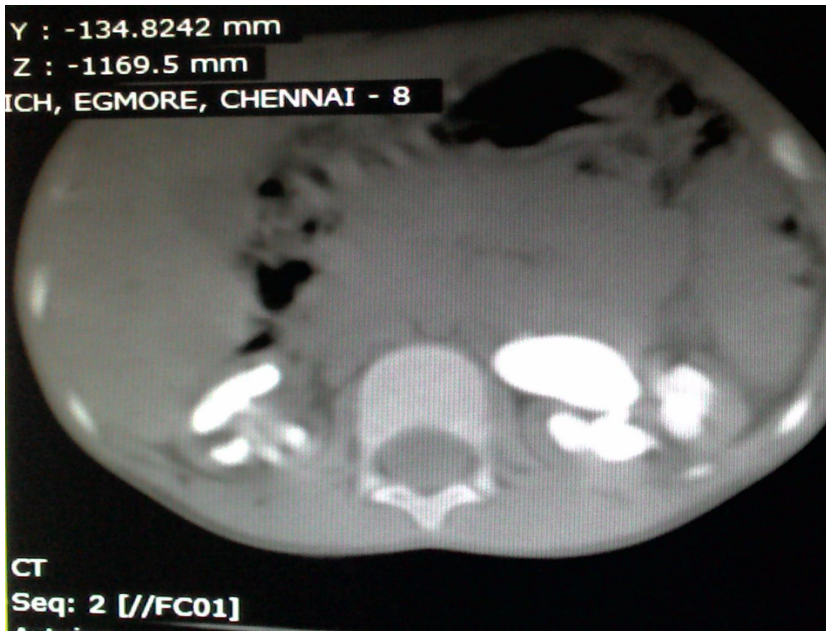


FIG 11 : CT scan showing of a 7 year old girl showing multiple bilateral pelvic and calyceal calculi.

However, the use of CT scan should be limited in children to difficult cases like small and faintly opaque ureteral stones as CT delivers significant irradiation.

NATURE AND CHARACTERISTICS OF STONE :

The appearance of a stone on imaging studies is dependent on its composition.

STONE TYPE	Xray / CT scan	DENSITY
Calcium oxalate	radio-opaque	very dense
Calcium phosphate	radio-opaque	very dense
Struvite stone	radio-opaque	Intermediate density
Cystine stone	radio-opaque	Intermediate density
Uric acid stone	Radiolucent	Low density
Indinavir stone	Variable lucency	Variable density

FIG 13: Table showing the appearance of different stones in x-ray/ CT scan

NEPHROCALCINOSIS:

Nephrocalcinosis denotes deposition of calcium oxalate or calcium phosphate in the tubulo-interstitial region of the kidney. Medullary nephrocalcinosis appears to be the more common pattern observed[8]. Nephrocalcinosis, though often seen with nephrolithiasis, may occur without its concurrence. Though the pathologies of the two are distinct, the risk factors of the two are the same [8]. It is also important to note that, of the two, nephrocalcinosis appear to be more commonly associated with renal dysfunction.

Nephrolithiasis when seen with nephrocalcinosis particularly suggests the presence of metabolic disorder like hyperoxaluria or distal renal tubular acidosis.The following table (Fig 14) shows the common causes of nephrocalcinosis.

COMMON CAUSES OF NEPHROCALCINOSIS

1. Prematurity
2. Hypercalcemia
3. Williams syndrome
4. Primary neonatal hyperparathyroidism
5. Paracellin I disorders
6. Bartter's syndrome
7. Dent's syndrome
8. Lowe syndrome
9. Cystinosis
10. Distal RTA
11. Calcium sensing receptor disorders
12. Primary hyperoxaluria
13. Cystic fibrosis
14. Drugs like frusemide, dexamethasone
15. Long term parenteral nutrition
16. Vitamin A and D intoxication

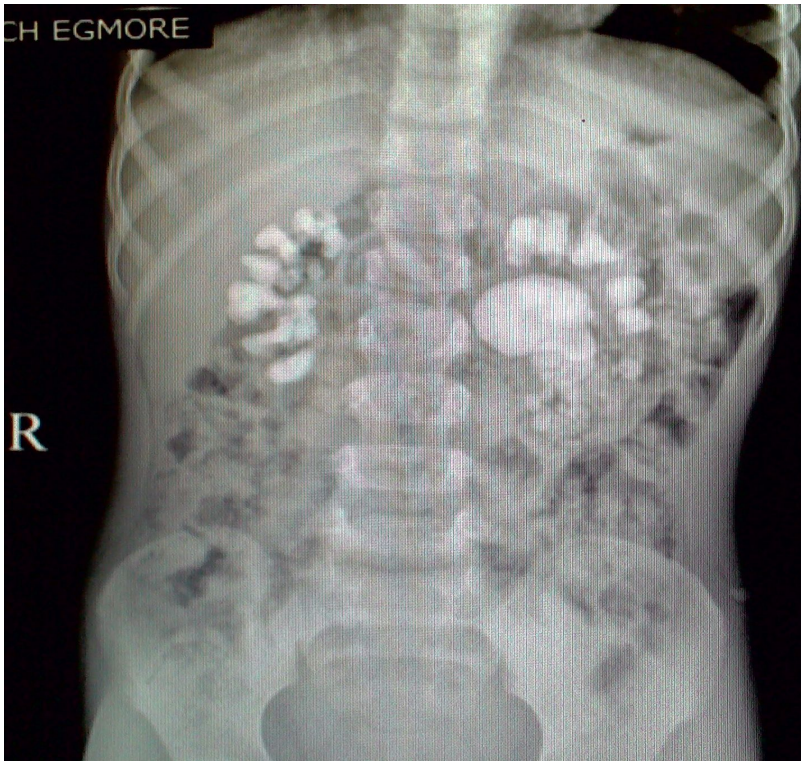


FIG 15: Plain Xray KUB showing bilateral nephrocalcinosis in a 8 year old boy

DIFFERENTIAL DIAGNOSIS FOR NEPHROCALCINOSIS:

1. Acute cortical necrosis
2. Chronic glomerulonephritis
3. Kidney transplant rejection
4. Pyelonephritis
5. Renal tuberculosis
6. Renal vein thrombosis
7. Tamm – Horsfall deposits

GRADING SCALE FOR MEDULLARY NEPHROCALCINOSIS IN CHILDREN	
GRADE I	Mild increase in echogenicity around the border of the medullary pyramids
GRADE II	Mild diffuse increase in echogenicity of entire medullary pyramid
GRADE III	Greater, more homogenous increase in echogenicity of entire medullary pyramid

TREATMENT OF UROLITHIASIS :

ACUTE MANAGEMENT OF STONE :

- Oral or parenteral analgesics for attacks of colicky pain .
- Calcium channel blockers and corticosteroids for facilitating stone passage

- If there is no obstruction, large fluid administration to facilitate stone passage
- Physical activity
- If there is obstruction, further evaluation of function of the kidney using renal scintigraphy (MAG-3) / intravenous urogram may be done.
- If obstruction persists, prompt removal of the stone to avoid kidney damage

SURGICAL INTERVENTIONS :

INDICATIONS :

- Stones more than 5 mm
- Symptomatic stones

Only cystine stones and uric acid stones can be dissolved chemically, cystine Stones by chelating agents and uric acid stones by alkalinizing urine and by administration of allopurinol.

RENAL STONES :

- Extracorporeal shock wave lithotripsy
- Percutaneous nephrolithotomy
- Open surgery

PROXIMAL URETER :

- Extracorporeal shock wave lithotripsy

DISTAL URETER :

- Retrograde ureteroscopic lithotripsy with holmium : YAG laser

FIG 16: Plain Xray showing right distal ureteral calculi

PRIMARY BLADDER STONES :

- Open surgery
- Endoscopic transurethral disintegration with mechanical cystolithotripsy

Recommendations For Interventional Management In Pediatric stones

Stone Size And Localisation	Primary Treatment	Secondary Treatment
Stag horn	PCNL	ESWL / Open
Pelvis <10 mm	ESWL	RIRS/PCNL
Pelvis 10 – 20 mm	ESWL	PCNL
Pelvis >20 mm	PCNL	ESWL/Open
Lower pole calyx <10 mm	ESWL	RIRS/PCNL
Lower pole calyx >10 mm	PCNL	ESWL
Upper ureter stones	ESWL	PCNL/URS/Open
Lower ureter stones	URS	ESWL/ Open
Bladder stones	Endoscopic	

(ESWL – extra corporeal shock wave lithotripsy, PCNL – percutaneous nephrolithotomy, URS – ureteroscopic removal of stones, RIRS- retrograde intrarenal surgery)

SPECIFIC THERAPEUTIC AND PREVENTIVE MEASURES :

HYPERCALCIURIA :

NUTRITION:

1. Low sodium diet
2. Avoidance of high protein diet (animal protein)
3. Avoidance of marked dietary excess of calcium (dietary calcium restriction may lead to negative calcium balance, and furthermore leads to increased absorption of oxalate, and thus results in oxalate stones)
4. High fluid intake
5. High fibre diet

PHARMACOLOGIC TREATMENT :

THIAZIDE DIURETICS :

Thiazide diuretics reduce renal excretion of calcium and thus cause hypocalciuria and improve bone density. Hypokalemia which is a side effect of thiazide diuretic, should be carefully avoided because hypokalemia may lead to hypocitraturia and thus causing an inadvertent increase of the urinary saturation.

Table : Hints at selection of patients for anticalcium stone therapy

Serum/ urinary defect found	**Therapy likely to succeed**
Hypercalcemic hypercalciuria with high PTH	Surgical removal of abnormal parathyroid
Hypercalcemic hypercalciuria with hypervitaminosis D	Stop excessive vitamin D
Hypercalciuria , immobilisation	Exercise , large fluid intake,avoiding excess calcium in diet
Hypercalciuria,hyperthyroidism	Treat hyperthyroidism
Hypercalciuria, hperabsorption	Neutral phosphates
Hypercalciuria,renal leak	Thiazides
Relative hypercalciuria, magnesium deficit(Mg*100/Ca)<=33	Magnesium oxide
Hyperuricemia and hyperuricosuria with calcium urolithiasis	Allopurinol
Intestinal hyperabsorption, hyperoxaluria	High calcium, very low oxalate diet plus cholestyramine

CITRATE :

Potassium citrate 0.2-0.3g/kg is given in patients with distal RTA, which leads to reduction in calcium excretion and increase in urinary citrate level and serum potassium level through correction of metabolic acidosis

PRIMARY HYPEROXALURIA :

NUTRITION :

1. High fluid intake

2. Special dietary recommendations are not needed except for avoidance of extremely oxalate rich food like spinach or rhubarb.

PYRIDOXINE :

High dose pyridoxine therapy of 5 – 10 mg/kg/day is recommended for primary hyperoxaluria type I.Trial of atleast 3 to 6 months is warranted. Pyridoxine therapy does not appear to of help in primary hyperoxaluria type II.

CRYSTALLIZATION INHIBITORS :

1. Citrate (0.1 – 0.2 g/kg/day)
2. Magnesium And Phosphate Preparations - inhibitors of calcium oxalate or calcium phosphate crystallization .

RENAL REPLACEMENT THERAPY :

It is needed in cases of primary hyperoxaluria and enteric hyperoxaluria. In case of primary hyperoxaluria, combined hepatic and renal transplantation will be of beneficial.

SECONDARY HYPEROXALURIA :

NUTRITION :

1. High fluid intake
2. Avoidance of oxalate rich food like spinach, rhubarb
3. Avoidance of excess intake of ascorbic acid (precursor for oxalate)
4. Calcium supplementation

CRYSTALLIZATION INHIBITORS:

1. Potassium citrate
2. Sodium potassium citrate
3. Magnesium
4. Neutral phosphate

DIET RICH IN OXALATE
1. Cocoa 2. Tea 3. Grape juice 4. Grapefruit juice 5. Apple juice 6. Almond 7. Cashew nuts 8. Cranberries 9. Currants 10. Raspberries 11. Plums 12. Greens 13. Rhubarb 14. Spinach 15. Beets

NEWER CONCEPT :

A promising potential treatment awaiting clinical confirmation is the use of Oxalobacter formigenes, an oxalate degrading anaerobic microbe that normally inhabits the intestine. Lending credence to the importance of such bacteria, it has been observed that patients with secondary hyperoxaluria have lack / absence of such bacteria.

CYSTINURIA :

1. High fluid intake (approximately 3 litres /day)
2. Low sodium diet
3. Alkalinization of urine
4. Avoid protein gluttony
5. Chelating agents :
    - D – penicillamine
    - Captopril
    - α mercapto propionyl glycine
    - Bucillamine (+ pyridoxine)

URATE STONES :

1. High fluid intake
2. Alkalinisation of urine

3. Avoidance of purine rich meat and excess proteins
4. Allopurinol (xanthine oxidase inhibitor)

STRUVITE STONES :

1. Surgery
2. Appropriate antibiotic therapy

Complete removal of the stone with subsequent sterilization of the urinary tract is the treatment of choice for patients who can tolerate the procedures. Percutaneous nephrolithotomy is the preferred surgical procedure for most patients with struvite stones. For some patients, ESWL in combination with percutaneous nephrolithotomy may be used. Open surgery may rarely be required. To reduce recurrence after surgery, irrigation of renal pelvis with hemiacridin (a solution that dissolves struvite) may be done.

Appropriate antibiotic therapy must be initiated based on the urine culture or the culture of stone fragments removed during surgery. Stone-free rates of 55–90% have been reported after surgical intervention.

For patients who are not candidates for surgical removal of stone, acetohydroxamic acid, an inhibitor of urease, may be tried. But

serious side effects like headache, tremor, thrombophlebitis have limited its use.

MEDICAL FOLLOW-UP:

Children with stones require close follow up, with frequent outpatient visits atleast once every 3- 4 months because they are unable to adhere to the preventive measure continuously without strict surveillance and emotional support from family and physician. Compliance to preventive and therapeutic measures must be ascertained during every visit through biochemical urinary monitoring if possible crystalluria on fresh urine.

FOLLOW UP IMAGING :

Plain x-ray and USG generally provide sufficient information for patient follow up. They must be performed at sufficient intervals depending on the type of stone, causal disease and presence or absence of crystalluria. In the absence of symptoms or crystalluria, one imaging per year seems sufficient.

IVP and CT scan can also be done to detect residual fragments when necessary.

The significance of identifying the underlying metabolic cause, lies in the fact that recurrence of stone can be avoided by treating the metabolic abnormality and also the most dreaded complication of end stage renal disease could be prevented by appropriate treatment at appropriate time. This can also help us and the family to understand the prognosis of the disease, especially in the case of inborn errors leading to renal stones (eg: primary hyperoxaluria), thereby aiding in avoiding the unnecessary time and money spent in treatment. Thus the scope of this study is to identify the prevalence of various metabolic parameters causing renal stones.

AIM AND OBJECTIVE

AIM:

To evaluate the metabolic abnormalities in children with urolithiasis.

OBJECTIVE:

PRIMARY OBJECTIVE :

To identify the metabolic parameters leading on to stone disease in pediatric patients by measuring the 24 hour urinary calcium, oxalate, citrate and uric acid.

SECONDARY OBJECTIVE :

i) To identify the mean age of presentation of children with urolithiasis.

ii) To identify the sex predilection in children with urolithiasis.

iii) To find the incidence of family clustering of stone disease.

iv) To find the most common way of presentation of pediatric urinary tract calculi.

REVIEW OF LITERATURE

The presence of stones in the urinary tract has fascinated medical scientists for centuries. Perhaps it is the preposterous idea that the human body should manufacture something so foreign and mundane as a stone that has caused the subject to be viewed more with humorous fascination than scientific erudition. In recent years, however, serious investigations have been conducted in the area of urolithiasis, clarifying some of the pathogenetic mechanisms involved in stone production.

Urinary stone incidence and composition have changed markedly over the past decade in parallel with profound changes in life style and dietary habits, resulting in a dramatic rise in the occurrence of calcium oxalate stones. However, studies in India, evaluating the metabolic abnormality in urinary calculi are very scarce.

In a prospective study conducted in Iran from 2005 to 2007 to evaluate the metabolic factors associated with urinary calculi in children, Mitra Naseri et al., subjected 142 children with renal stones to

imaging studies, serum biochemical analysis and 24 hour urine analysis for calcium, oxalate, citrate, uric acid, magnesium and the results were as follows . [41]

Hypercalciuria - 17.6%

Hyperuricosuria - 16.1%

Hyperoxaluria - 11.9%

Cystinuria - 6.3%

Hypocitraturia - 2.1%

Mixed abnormalities - 11.2%

Idiopathic - 46.2%

From their study, they concluded that calcium and uric acid abnormalities were the most common metabolic problems leading onto stone disease, and that vesico-ureteric reflux was the most common anatomical abnormality causing renal calculi in their study group.

This is, by and large, in contrast to a study done by Akhil Joshi et al., from Sanjay Gandhi PG institute of medical sciences, Lucknow [42] . They analysed 39 patients with first episode of renal calculi, for various parameters including serum calcium, phosphorus, creatinine, albumin, alkaline phosphatase, parathyroid hormone, 25 –

hydroxy vitamin D levels, and 24 hour urinary citrate, oxalate, calcium, uric acid, and ammonium chloride loading test, if at all needed (to rule out distal renal tubular acidosis). The following is the result of the study.

Hypocitraturia - 82%

Hyperoxaluria - 56%

Hypercalciuria - 41%

Incomplete RTA – 5%

Idiopathic – 3%

Considering that majority of first time renal stone formers have metabolic abnormality and that hypocitraturia as the most common one detected, they suggested that insufficency of inhibitors, especially citrate, is the main culprit behind the renal stones.

These results were similar to that observed in a study titled "Twenty-Four-hour Urine Constituents in Stone Formers", conducted by N.S.Hussain et al., from Malaysia, in which 106 patients with renal calculi were included and their 24 hour urine samples were analysed for calcium, citrate, urate and oxalate,and they observed that the commonly associated biochemical abnormalities were hypocitraturia , hyperoxaluria and hypomagnesuria[43].

Kristin J. Bergsland et al., from the University of Chicago, in his study to identify the metabolic abnormalities in stone forming children, compared chemical measurements and crystallization properties of 24-hour urine samples from 129 stone forming children, with 105 non-stone forming siblings and 183 normal, healthy children with no family history of stones; in age group of 6 to 17 years. They identified hypercalciuria and the reduction in the gap between upper limit of metastability and supersaturation of calcium phosphate, as crucial determinants of stone risk [44] .

In a retrospective study done by Afshin Safaei et al., from Iran, from 2004 – 2009, it was observed in a group of 84 children that

(i) Kidney is a more common site for calculi than the bladder.

(ii) Most common presenting symptom observed in the study was dysuria, abdominal pain and restlessness

(iii) Positive family history being a significant risk factor followed by urinary tract infection and structural abnormality

(iv) Normocalcemic hypercalcuria takes lead among the metabolic factors, followed by hyperuricosuria, hyperoxaluria, cystinuria [45] .

Ismail Dursen et al from turkey found that out of the 179 pediatric patients included in their study from 1998-2005, hypercalciuria and hyperuricosuria were detected in 42.3 and 54.8% respectively [46] .

Interesting to quote here will be the results of the case control study done by Kumar et al from India, from 1999 to 2001. He stated that hypocitraturia is the most common cause for pediatric renal stones followed by hyperoxaluria. The study included 125 subjects, of whom 44 first time stone formers & 56 recurrent stone formers were taken as cases, and 25 healthy staff members were taken as controls. He found that 24 hour urinary oxalate and calcium concentration were consistently higher in stone formers when compared with normal individuals. Stone patients excreted significantly higher levels of uric acid. Patients with recurrent stone formation excreted significantly high levels of calcium ($p < 0.05$) and lower levels of citrate ($p < 0.01$) than patients with one episode of stone formation [47] .

There are significant number of studies evaluating the effect of age and gender on the distribution of different types of urinary calculi. Notable among them is a study on 27,980 renal stone patients (19442 males and 8538 females) by Daudon et al., from 1976 to 2001, who analyzed the relationship between age and sex and composition of stone. He found a male preponderance for calcium oxalate and urate stones, and female predominance for calcium phosphate and struvite stones, and an increasing prevalence of urate stones with age in both males and females [48].

A majority of patients with urinary calculi remain asymptomatic over 3–5 years follow up. In a study from Japan, it was observed that after a mean follow up of 33 months, 12% of Japanese patients who were asymptomatic, required urological management. A Canadian study showed that after a mean follow up of 32 months, 32% of Canadian patients with asymptomatic urolithiasis developed urinary colic, with a cumulative 5-year event probability of 48.5% [49]

Novak et al., conducted an epidemiologic investigation to identify the sex prevalence of pediatric renal stones in united states. They observed that boys were more commonly affected in the first decade of

life and girls in the second decade [50] . The reason for this unique epidemiologic finding is not readily apparent necessitating the need for further studies in this topic.

Dwyer et al., from Mayo clinic conducted a population based study in pediatric population to determine the incidence of symptomatic renal stones during a 25-year period and also to identify factors related to changes in stone incidence during that period . A total of 207 children were included in the study and they observed that the incidence rate increased by 4% per calendar year (p value - 0.01) throughout the 25-year period. The exact cause of this finding could not be determined by this study. [51]

Mohsen Akhavan et al., [52] from Iran conducted a case series with 100 pediatric patients for evaluation of etiology and clinical manifestations of renal stones in Qom. 100 Children, younger than 14 years old with mean age of 3.32 years, were included in the study. 54% of them were males. Etiology of renal stones in 5% was unclear. Metabolic disorders found in patients were hypocitraturia in 54 %, hyperoxaluria in 14 %, hyperuricosuria in 25%, cystinuria in 6%, hypercalciuria in 28% and phosphaturia in 8% of patients. The presenting clinical feature was

fever, pain, dysuria, irritability and hematuria. Family history of urolithiasis was found in 23% of patients. 54% of children presented with urinary tract infection (UTI). They concluded that majority of patients were symptomatic and the commonest risk factor being hypocitraturia among others.

The incidence of renal stones is on the increase throughout the world. Sas et al.,[53] documented a significant increase in the incidence of renal stones in children between 1996 and 2007, on the basis of his study in the state of South Carolina. They noticed the greatest rate of rise in adolescents, pre-adolescents, and Caucasian children. They also found that infants, toddlers, and African-American children did not show significant increase in incidence in that period. Girls showed a growing predominance in their population.

Stone composition and urinary metabolic stone risk parameters in children are distinct from those of adults. Though renal stone formation has a linear relation with the age of the patient, pediatric patients tend to form a greater percent of calcium-based stone than adults. On the other hand, there are fewer cases of uric acid stones in children than adults. The reason for this discrepancy is associated with a higher

urinary pH in pediatric population than in adults. It was noted that the risk of childhood struvite stones has decreased, perhaps due to the advancements in diagnosis and management of urinary tract infections and management of anatomical and neurological factors associated with urinary infections [54] .

Owing to the recent rise in incidence of childhood obesity, it has long been assumed that large BMI contributes to the childhood stone disease epidemic. A recent study by Kieran *et al.* however questions the existence of such a link in children. The authors stratified 112 children with urolithiasis based on their BMI into patients with lower percentile body weight, normal weight, and upper percentile body weight. They observed that upper percentile body weight was not found to be associated with earlier stone development or larger stone size or with the need for multiple surgical procedures. The surgical intervention rate and stone size were similar regardless of body mass index [55] .

This was further confirmed by the case control study conducted by Kim *et al.*, who compared 110 pediatric cases with urolithiasis to 396 appropriately matched controls in his study and reported no association between high BMI and urolithiasis [56] .

In his study to identify the association of systemic conditions with urolithiasis in children, Kokorowski et al., used ICD 9 codes to identify urolithiasis cases from 2004 to 2009, using Pediatric Health Information System Database. Diagnoses from all hospital encounters were ascertained for comorbid illnesses. Univariate and multivariable conditional logistic regression were used to assess the associations of urolithiasis with diabetes mellitus, hypertension and obesity. Among pediatric patients included in their study, urolithiasis is associated with higher odds of obesity and hypertension and lower odds of type I diabetes mellitus [57].

Thus it is clear that pediatric urolithiasis differs widely in different regions in various parameters. The results of 24 hour urine analysis for metabolic parameters are found to vary largely. However, the importance of deficiency of inhibitors in causing urolithiasis is recently well accomplished. Supplementation of inhibitors has proved beneficial in many trials. It must clearly be borne in mind that urolithiasis is just a symptom and the cause for it must definitely be sought for.

Materials and Methods

STUDY DESIGN : Prospective Descriptive study

STUDY PLACE : Department of Pediatric nephrology,
Institute of Child Health and Hospital for children,
Egmore

STUDY PERIOD : April 2014 – September 2014

SAMPLE SIZE : 50

CASE DEFINITION:

All children with urinary tract calculi, presenting in the nephrology outpatient department of our hospital, satisfying the inclusion criteria were taken for the study.

INCLUSION CRITERIA :

All children between 1 month and 12 years

- with the presence of a stone on imaging by ultrasonography / Xray / CT scan
- documented episode of microscopic hematuria due to renal stone or passage of crystals in urine.

EXCLUSION CRITERIA:

Age < 1 month or > 12 years

MANOEUVRE:

- Ethical committee and Scientific committee approval were obtained before commencing the study.
- Informed consent was obtained from the parents or the primary caregivers of the children.
- All patients fitting the inclusion criteria were selected.
- Detailed history regarding the presenting symptom, family history, mode of diagnosis and intervention performed was recorded.
- If the child had urinary tract infection, the same was treated and then the child was evaluated for renal stones after a month.
- Subjects who were on pharmacologic doses of vitaminD, calcium, antacids,diuretics, potassium citrate and vitamin C were asked to discontinue the medications for at least one 1 week, after which the metabolic evaluation was done.
- An exception to this, is patients with distal renal tubular acidosis, where we could not discontinue drugs

for prolonged period, we admitted the children and discontinued the drugs under supervision. Though the cause for renal stones in distal renal tubular acidosis is already known as hypercalciuria and hypocitraturia, 24 hour urinary metabolic evaluation was carried out.

- If the child had undergone any surgical procedure, the child was evaluated 3 months later.
- Ultrasonography and x-ray KUB were done for all patients with renal stones. For patients who had no finding of stone in ultrasonography but having strong suspicion of stone due to microscopic hematuria or renal colic, CT scanning was done.
- About 3 ml of blood was collected for blood investigations comprising of renal function test, calcium, phosphorus, magnesium, alkaline phosphatase, uric acid.
- If the child had abnormal calcium or phosphate levels, vitamin D and parathyroid hormone levels were measured.

- If renal tubular acidosis was suspected, then arterial blood gas analysis was done to document acidosis.
- 24 hour urine collection was done for measurement of citrate, calcium, oxalate and uric acid and the tests were done at main Apollo hospital laboratory, Chennai
- Early morning urine pH was done for all patients .
- To rule out cystinuria, urine sodium nitroprusside test was done for all patients and if it turned out to be positive, urine aminoacid chromatography was done to confirm the diagnosis.

NORMAL VALUES :

	AGE	RATIO SOLUTE/CREATININE	24 HOUR URINE EXCRETION
CALCIUM	0-6 months 7-12 months ≥2 years	<0.8 mg/mg <0.6mg/mg <0.21 mg/mg	<4 mg/kg/day
OXALATE	0 to 6 months 7 to 24 months 2 – 5 years 5 – 14 years >16 years	288 to 260 mg/g 110 to 139 mg/g 80 mg/g 60 to 65 mg/g 32 mg/g	<45 mg/1.73 m^2/day
CYSTINE	< 1 month 1-6 month >6 month	<180 mg/g <112 mg/g <38 mg/g	<60 mg/1.73 m^2/day
URIC ACID	Term infant >3 years	3.3 mg/dl GFR <0.53 mg/dl GFR	<815 mg/1.73 m^2/day
CITRATE	0 to 5 years >5 years	>0.2 – 0.42 g/g >0.14 – 0.25 g/g	> 0.14 g/1.73 m^2/day
MAGNESIUM	>2 years	<0.12 mg/mg	<88mg/1.73 m^2/day

Metabolic evaluation for renal stones comprises of following investigations.

IMAGING :

- Ultrasonography
- Plain Xray (KUB)
- CT abdomen (as and when needed)
- Intravenous pyelography (as and when needed)

URINE :

- In infants and nontoilet-trained patients, a random urine sample was checked for creatinine, calcium, uric acid, and oxalate levels.
- In toilet trained patients, 24-hour urine was collected for the measurements of calcium, oxalate, uric acid and citrate.
- Urine PH
- Urine sodium nitroprusside test
- Urine microscopy (routine / crystals)
- Urine culture

BLOOD :

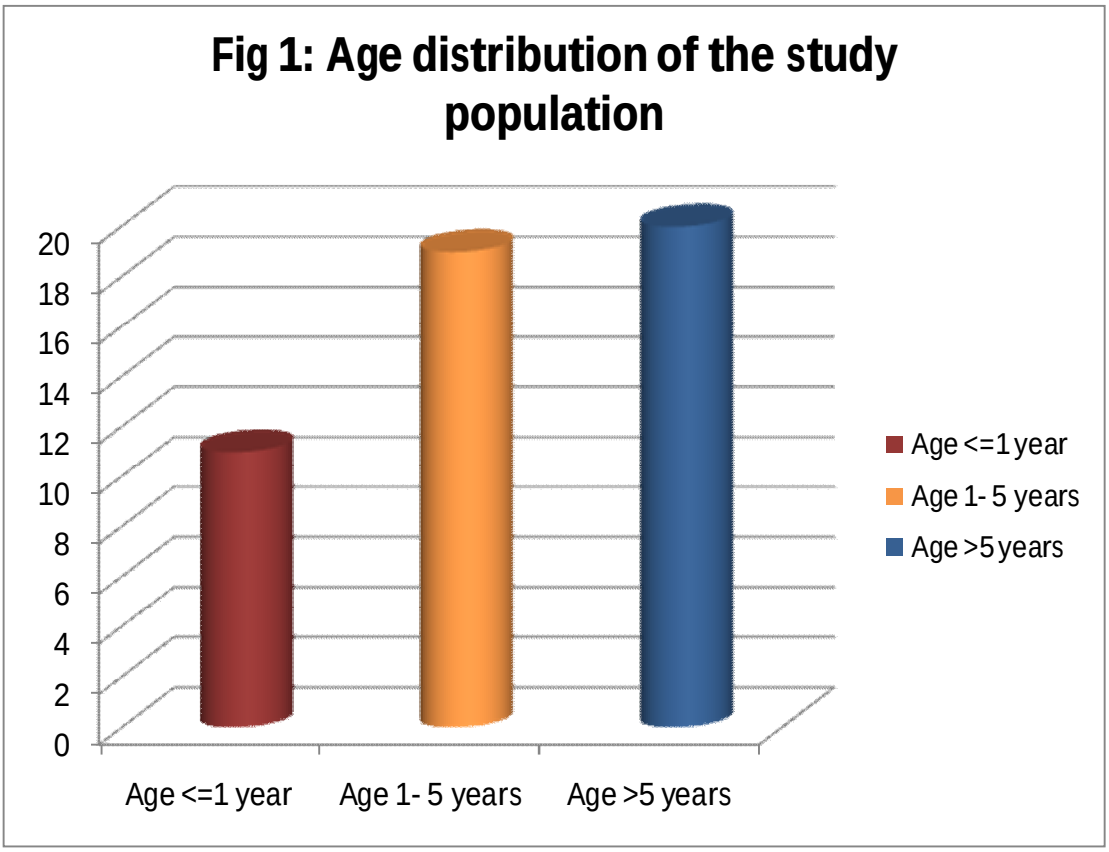
- Blood urea, s.creatinine, electrolytes
- Calcium, phosphorus, magnesium
- Alkaline phosphatase
- Uric acid
- PTH and Vitamin D (as and when needed)
- Arterial blood gas analysis (as and when needed)

RESULT ANALYSIS :

- The statistical analysis was done using SPSS version 15.0.
- Descriptive statistics were computed for all biochemical variables, for each of the diagnostic categories.
- A two-tailed *P-value* <=0.05 was considered statistically significant.

RESULTS

Our sample consisted of 50 children with age ranging from 2 months to 12 years. Mean age of presentation was 5.24 years (SD=3.28 yrs). 30 children were 5 year old or below. Out of these, 11 children were 1 year old or below.



Out of the 50 children included in our study, 17 were girls and 33 were boys. The following table shows the frequency and percentage of boys and girls in the study population.

TABLE 1:

	Number (n= 50)	**Percentage (%)**
Girls	17	34
Boys	33	66

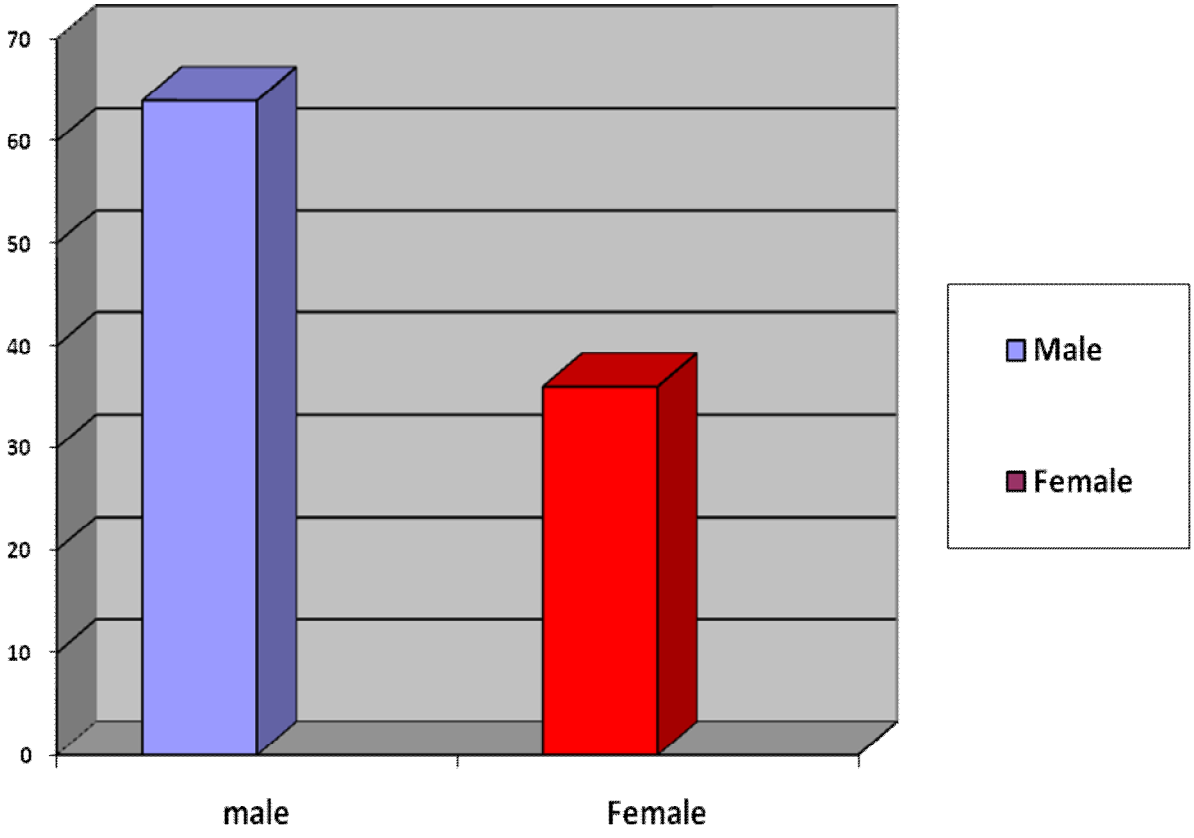
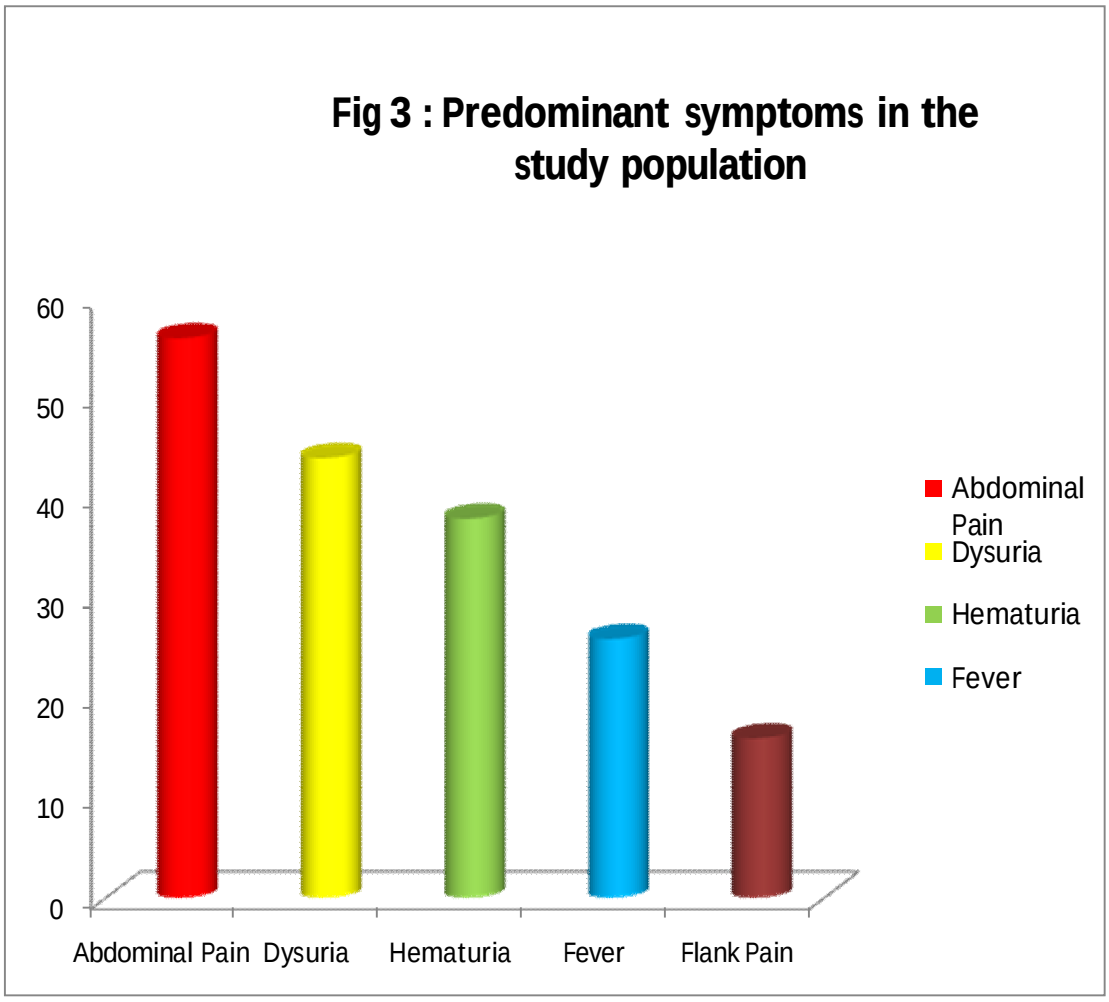


Fig 2. Gender distribution of the study population

The main presenting symptom was abdominal pain in 56 %, dysuria in 44%. Hematuria was present in 38% of children in the study group. Fever was present in 26% of patients and flank pain in 16 % of children.

TABLE 2 :

Presenting symptom	**Frequency (n=50)**	**Percentage (%)**
Abdominal pain	28	56
Dysuria	22	44
Hematuria	19	38
Fever	13	26
Flank pain	8	16
Vomiting	6	12
Increased frequency of micturition/ dribbling	6	12
Growth retardation	2	4

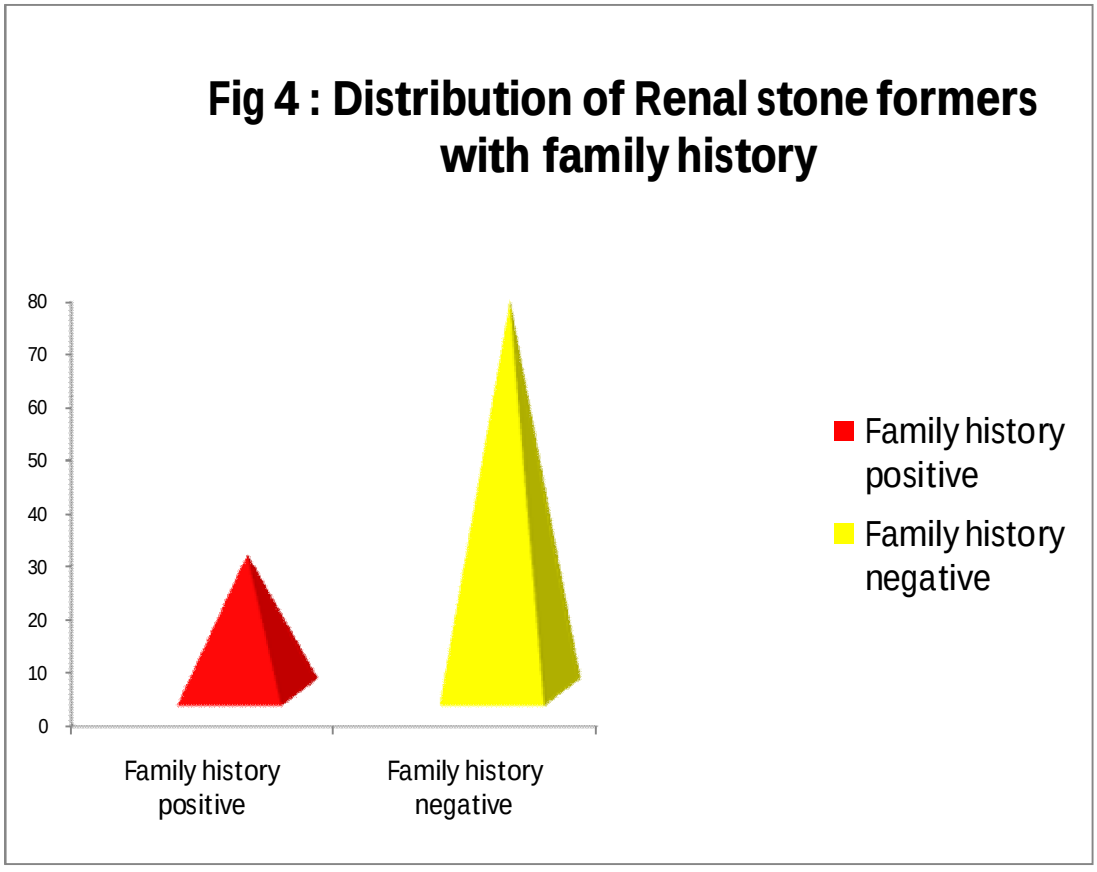


In children below 5 years, dysuria was the more predominant presenting complaint. About 1/4th of the patients were asymptomatic and were diagnosed coincidentally during imaging for other reasons, or by microscopic hematuria or passage of crystals in urine. 5 patients in our study had passage of crystals in urine and stone analysis was done for those patients and 2 patients had microscopic hematuria.

37 children had no family history of urolithiasis, whereas 13 children had positive family history in parents, siblings or close relatives.

TABLE 3:

	Frequency (n=50)	**Percentage**
Family history present	13	26
Family history absent	37	74



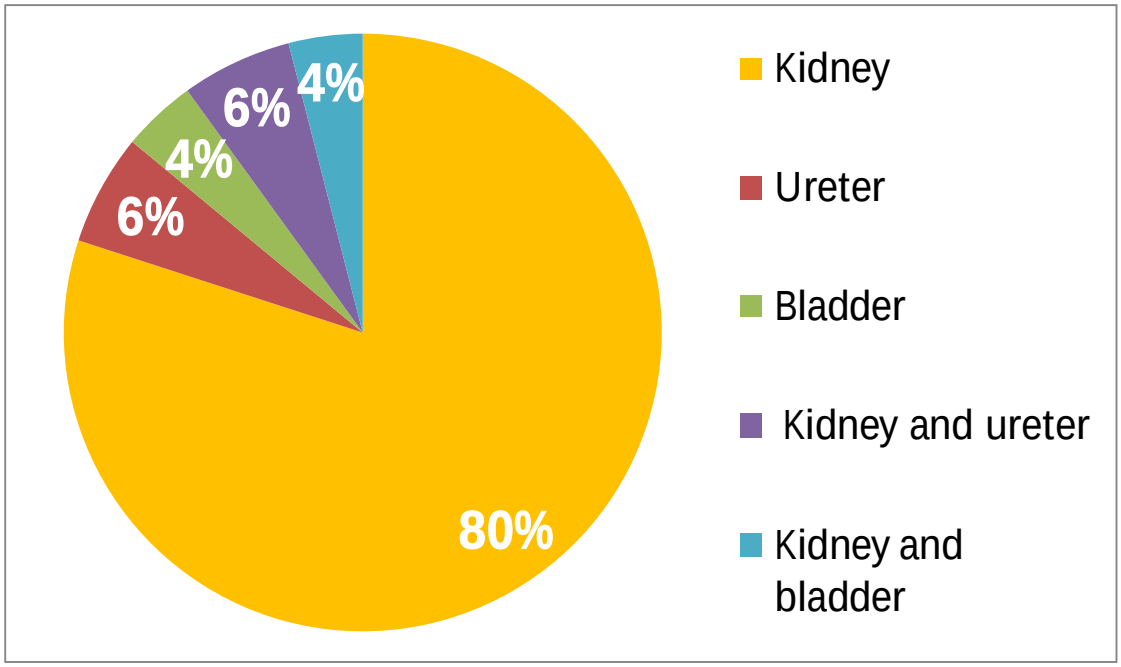
Ultrasonography of abdomen and KUB was done for all patients in our study group. Of the 50 children, 40 children had stones in the kidney, 3 children had stones in the ureter, 2 children had stones in the bladder, 3 children had stones in both kidney and ureter, and 2 children had stones in both kidney and bladder.

Location of calculi	**Frequency (n=50)**	**Percentage (%)**
Kidney	40	80
Ureter	3	6
Bladder	2	4
Kidney and ureter	3	6
Kidney and bladder	2	4

TABLE 4 :

Table showing the frequency and percentage of stones at various locations

FIG 5 : Pie diagram showing the percentage distribution of stones in various locations.



It was also found that the out of the 40 patients with renal stones, the calculi were unilateral in 23 children and bilateral in 23 children. In children with unilateral stones, right kidney calculi was in 14 children and left kidney calculi was in 9 children.

TABLE 5:

	Frequency (n=50)	Percentage
Renal Stone- unilateral	23	46
Renal Stone- bilateral	23	46

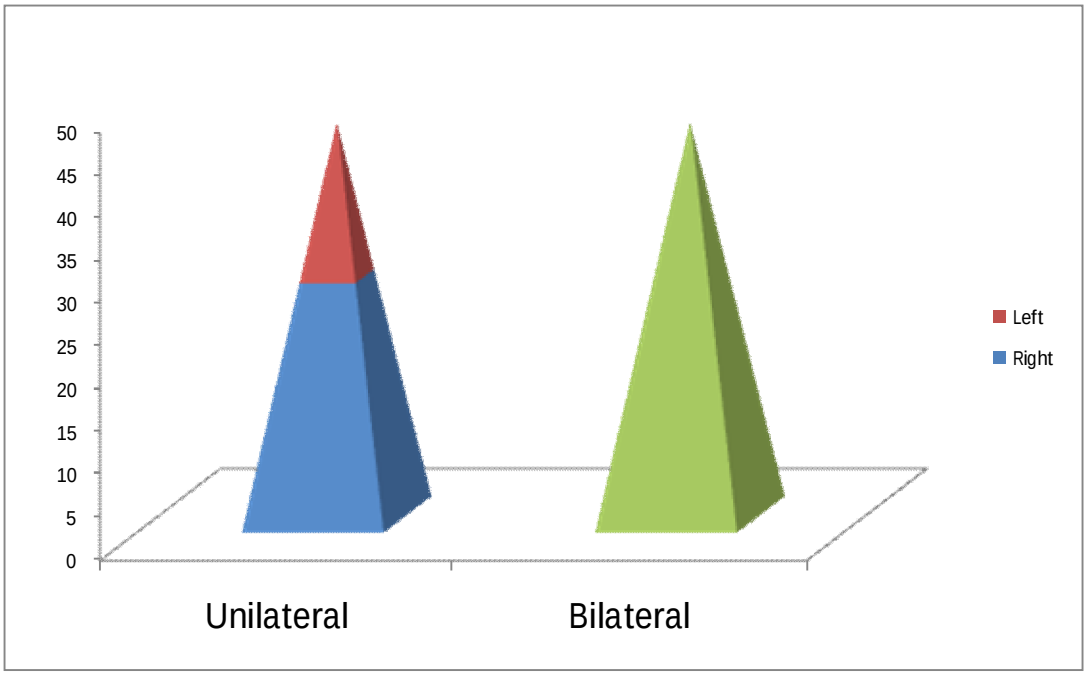
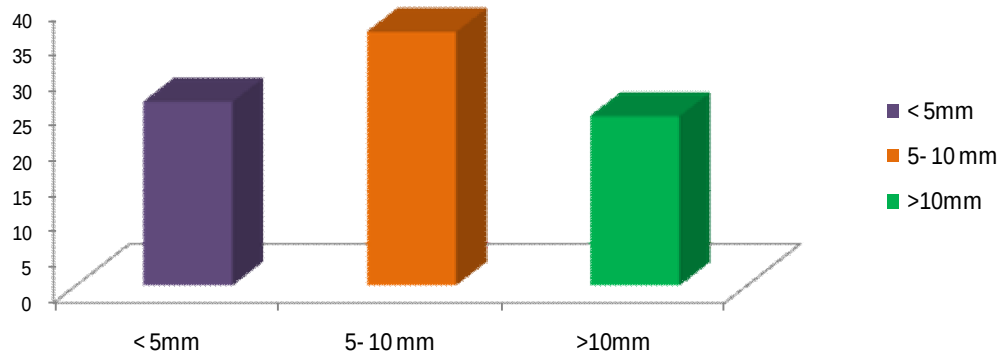


Fig 6: Distribution showing the location of renal calculi

24 children had single calculi, whereas multiple calculi was found in 21 children. The mean stone size in our study population was 8.93 mm (SD= 4.24mm) ranges from 3mm to 31mm. 13 patients had stone size < 5mm, 18 patients had stone size between 5 and 10 mm and 12 patients had >10 mm stones.

Fig 7 : Percentage distribution showing the size of the renal calculi in study population



This diagram shows the comparison of stone size in relation to gender in which the mean stone size of female was 9.27mm and in male it was 8.73mm with (p value=0.77) which was greater than 0.05 showing statistically insignificant relationship between gender and stone size.

Fig 8 : Comparison of Stone size in relation to gender

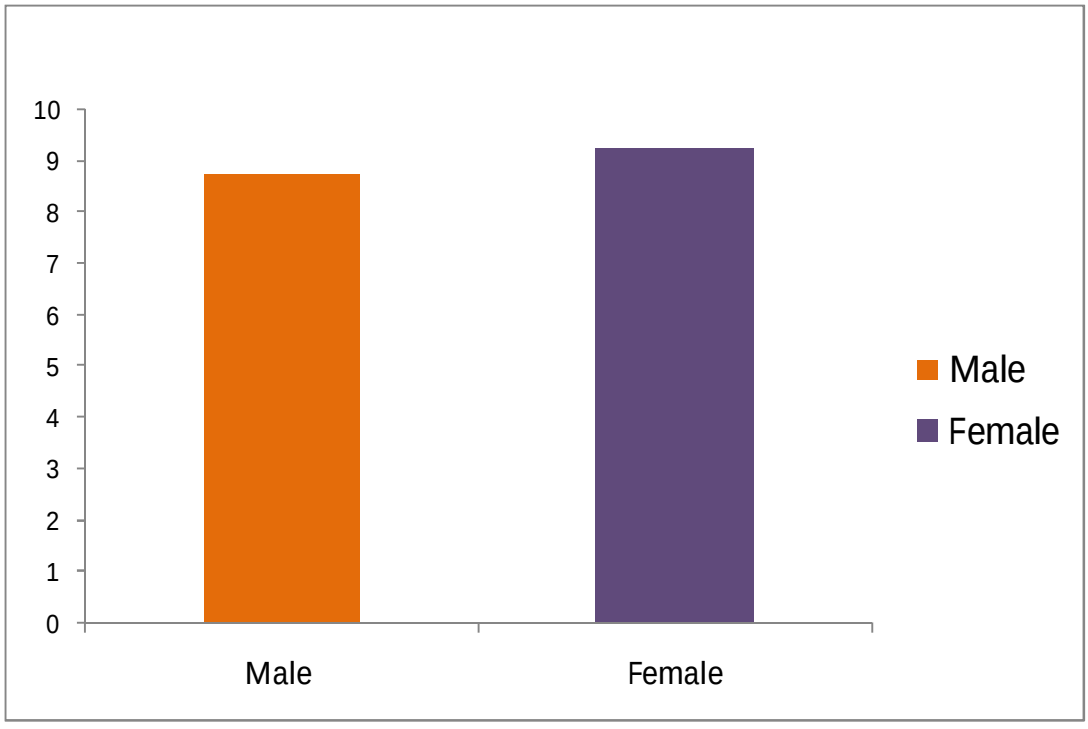
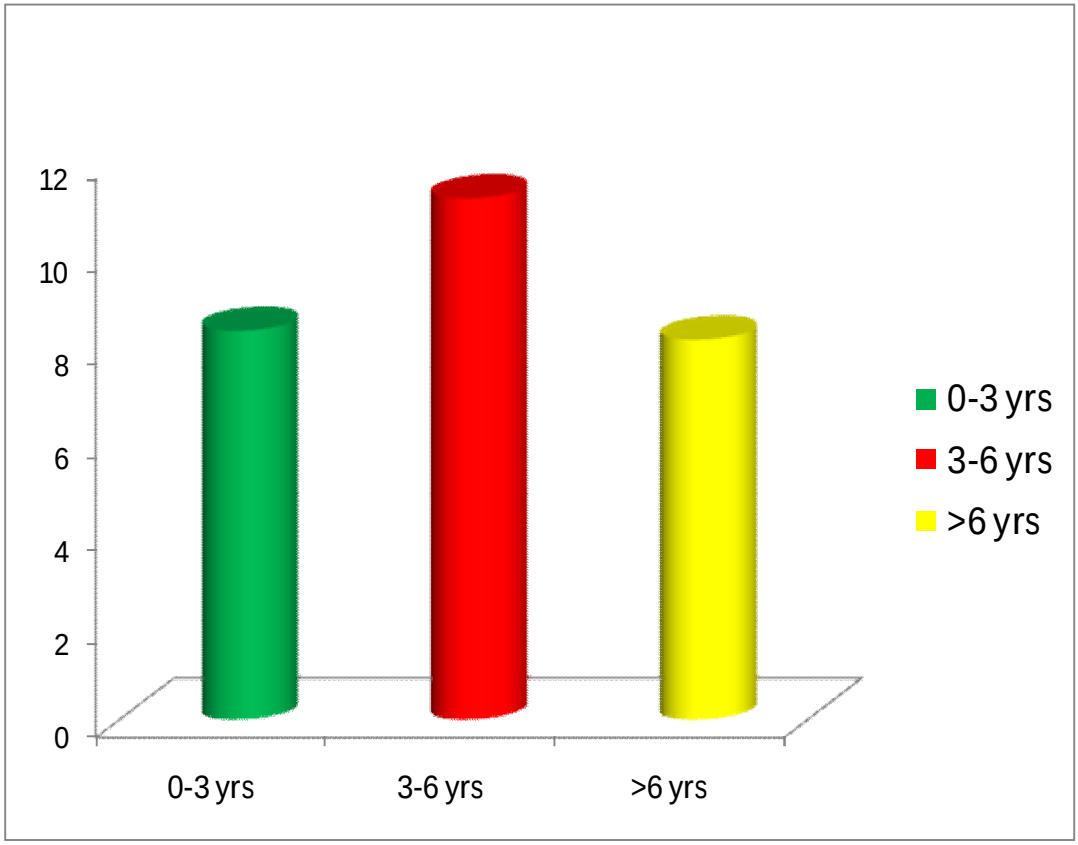


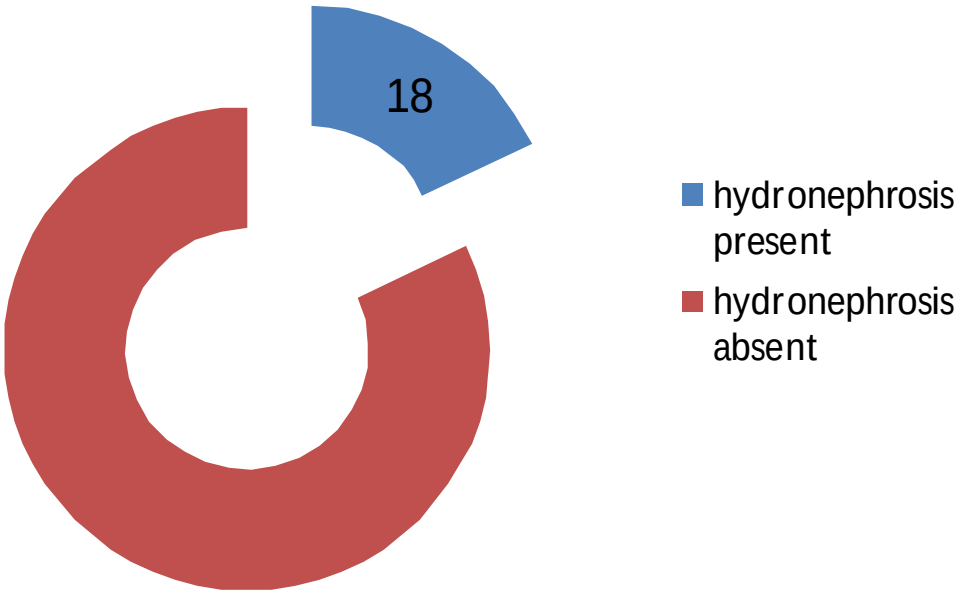
Fig 9 : Comparison of Stone size with age of the patients



This diagram shows the comparison of stone size in relation to age of the patients. They were categorized into three groups as 0-3 yrs, 3-6 yrs, <6 yrs. The mean stone size in 0-3 yrs was 8.38mm, 3-6 yrs was 11.22 mm, <6mm was 8.19mm. The p value was found as 0.38which was greater than 0.05 demonstrating that the relation between stone size and age is statistically insignificant .

Ultrasonography also showed the presence of hydronephrosis / hydroureteronephrosis in 9 patients. Nephrocalcinosis was present in 4 of the children. 2 out of the 4 children with nephrocalcinosis had distal renal tubular acidosis. Anatomical abnormalities were present in 3 patients. 1 patient had horse-shoe kidney and 2 other patients had posterior urethral valves.

Fig 10. Distribution showing the incidence of hydronephrosis in study population



Stone analysis was done in 5 patients. All 5 had calcium stones, of whom 2 patients had calcium oxalate stones,1 patient had calcium oxalate and calcium carbonate stones, 1 had calcium oxalate and amorphous phosphate, 1 had calcium, uric acid, ammonia and phosphate stone.

STONE ANALYSIS :

TABLE 6:

Stone analysis	**Number of patients (n =5)**
Calcium oxalate stones	2
Calcium oxalate and calcium carbonate stones	1
Calcium oxalate and amorphous phosphate	1
Calcium, uric acid, ammonia and phosphate stone	1

24 hour urinary metabolic workup was done in all patients of the study group and the results were as follows.

Hyperoxaluria was present in 26 patients, of whom 12 patients had hyperoxaluria alone while the rest 14 patients had mixed abnormalities.

Hypercalciuria was present in 16 patients totally, of whom only 4 patients had isolated hypercalciuria. In the rest 12 patients, mixed abnormalities were present.

16 patients had hyperuricosuria, 5 of whom are pure hyperuricosuric, while the rest 11 are mixed.

2 patients with nephrocalcinosis had hypercalciuria with hypocitraturia. These 2 patients also had low bicarbonate, normal anion gap metabolic acidosis and alkaline urine ph. A diagnosis of distal renal tubular acidosis was made in these 2 patients.

The following table shows the distribution of patients based on various metabolic abnormalities.

TABLE 7 :

METABOLIC ABNORMALITY	FREQUENCY	PERCENT
Hyperoxaluria	12	24.0
Hypercalciuria	4	8.0
Hyperuricosuria	5	10.0
Hypocitraturia	5	10.0
Hypercalciuria/hyperoxaluria	5	10.0
Hyperoxaluria/hyperuricosuria	4	10.0
Hypercalciuria /hyperuricosuria	1	2.0
Hypercalciuria/hyperoxaluria/hyperuricosuria	5	10.0
Hypercalciuria/ Hypocitraturia	2	4.0
Idiopathic	3	6.0

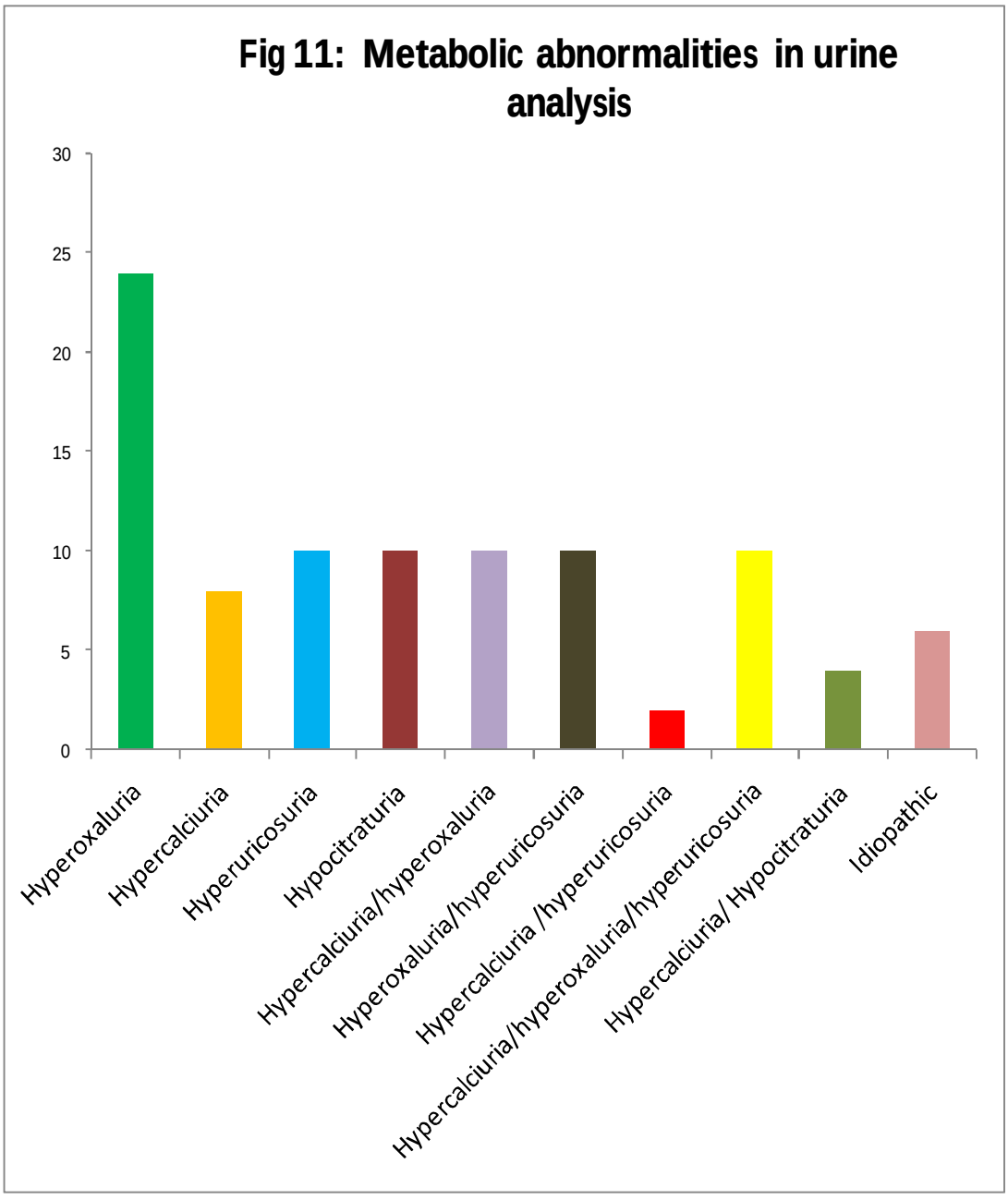


Fig 11: Metabolic abnormalities in urine analysis
30
25
20
15
10
5
0
Hyperoxaluria
Hypercalciuria
Hyperuricosuria
Hypocitraturia
Hypercalciuria/hyperoxaluria
Hyperoxaluria/hyperuricosuria
Hypercalciuria /hyperuricosuria
Hypercalciuria/hyperoxaluria/hyperuricosuria
Hypercalciuria/ Hypocitraturia
Idiopathic

COMPARISON OF PARAMETERS BETWEEN PATIENTS WITH HYPEROXALURIA AND HYPERCALCIURIA.

HYPEROXALURIA :

Out of 50 children included in our study, 26 children had hyperoxaluria. The mean age of presentation in patients with hyperoxaluria was 4.69 years with standard deviation of 2.72 years. Family history was positive in 23% of children with hyperoxaluria. Out of the 26 children, 15 were boys and 11 were girls. Mixed abnormalities were present in 14 children and isolated hyperoxaluria was present in 12 children.

TABLE 8 :

PARAMETERS	HYPEROXALURIA
Number of patients	26
Mean age of presentation	4.69 years ± 2.72 years
Family history	23%
Male : female ratio	15:11
Mean Stone size in mm	7.42 mm ± 2.77 mm
Mixed abnormalities	14

HYPERCALCIURIA :

In our study population 17 children had hypercalciuria. 4 children had hypercalciuria as an isolated abnormality, whereas remaining 13 children had mixed abnormalities with hypercalciuria as a component. Out of the 17 children, 8 were boys and 9 were girls. Mean age of presentation of children with hypercalciuria was 4.71 years with SD of 2.90 years. Family history was positive in 12.5 % of children with hypercalciuria.

TABLE 9 :

PARAMETER	HYPERCALCIURIA
Number of patients	17
Mean age of presentation	4.71 years ± 2.90 years
Family history	12.5%
Male : female ratio	8:9
Mean Stone size in mm	7.642mm ± 2.82 mm
Mixed abnormalities	13

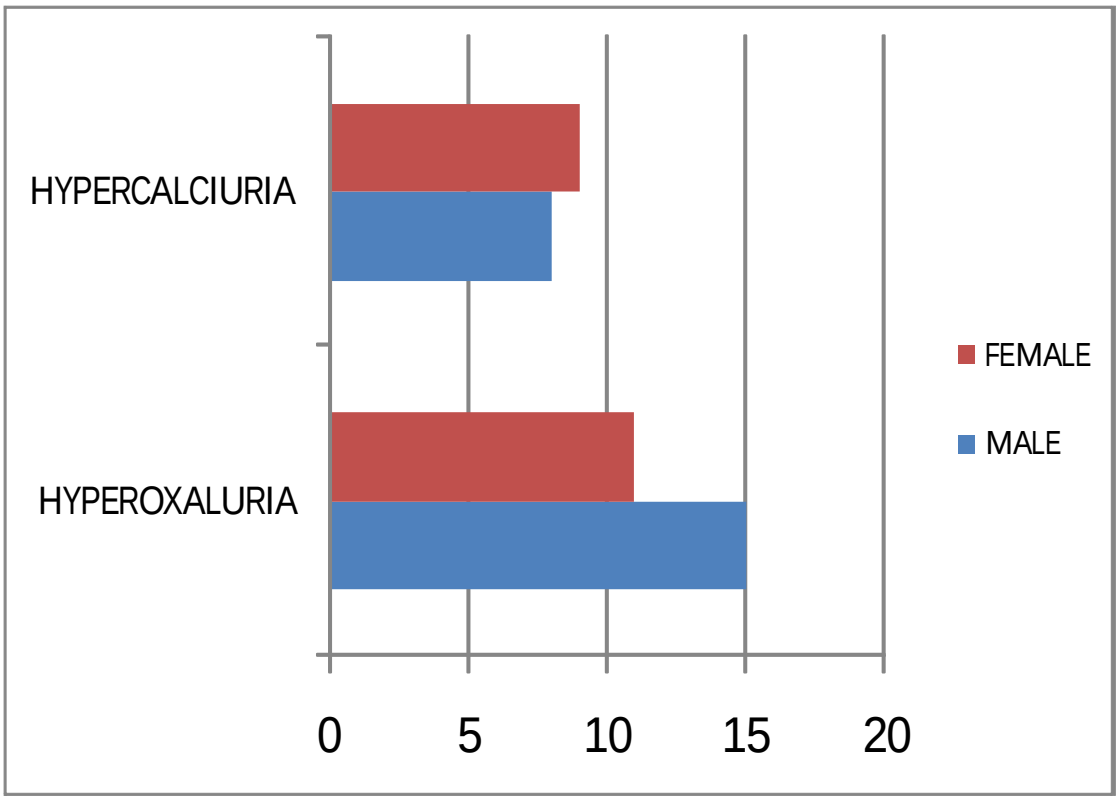


FIG 12: Bar chart showing the gender distribution of children with hyperoxaluria and hypercalciuria.

When we compared the proportion of males and females in children with hyperoxaluria and hypercalciuria, there was no significant difference (p value =0.344) showing that the relation between gender and type of metabolic abnormality is insignificant.

Urine culture was positive in 2 patients, of whom one patient had E.coli growth and the other had proteus growth. None of the patients had family history of cystinuria / passage of cystine stones in urine. Urine sodium nitroprusside test was done in all patients and none of the patients had positive result.

DISCUSSION

Urolithiasis is not an uncommon problem in childhood. Delay in the diagnosis or treatment of stone disease, may lead to damage of renal parenchyma and thus result in end stage renal disease. The true incidence of stone disease in Indian children has not been identified. Considering the volume of referred patients with urolithiasis to the pediatric outpatient department of our hospital, pediatric renal stone disease appears to be a disease of considerable burden.

The mean age of our patients at presentation was 5.24 years ± 3.28 years. In a study conducted in Iran with a population of 100 children the mean age at presentation was 3.32 years. In our study group, 30 children were 5 years old or below at presentation. Out of these, 11 children were 1 year old or below. The wide demographic variation of patients with calculus disease may be due to the different climatic, genetic, dietary and socio-economic factors.

Urolithiasis was detected more commonly in males, with the male to female ratio of 1.94:1. In most studies, the results were similar to

our study, with childhood renal calculus disease being more common in males. The male to female ratio of childhood renal calculus disease in different studies are found to be varying from 1.3:1 to 4:1.

Pediatric urinary stone formers have a different pattern of presentation when compared to adults. While non-specific symptoms such as dysuria and irritability are commoner in infants, abdominal pain is the predominant presentation in children >5 years. Hematuria, fever and flank pain are other common symptoms noticed in our study population. This is similar to the study conducted in Iceland and other countries, who demonstrated abdominal pain to be the most common presenting symptom accounting for > 50 %. It would be difficult to identify typical renal colic in children as against in adults.

In literature, the incidence of urinary tract infection in children with urolithiasis is reported to be between 8 % and 70 %. The rate of occurrence of urinary tract infection in our study population appears to be very low, when compared to these reported series. However, the actual role of UTI in urolithiasis is not clear, as the urinary

calculus can predispose the child to urinary infection by causing stasis, and conversely, UTI with urea splitting organisms can lead to formation of renal calculi such as magnesium ammonium phosphate stones.

In this case study, the location of calculi was comparable to that reported from developed countries. 96 % of the calculi in our study population were in the upper urinary tract and 4 % of children had primary bladder calculus. This result is very close to the recent studies from other countries, which have reported much lower rates of calculus in the lower urinary tract. During the past few years, the pattern of calculus disease has changed, in many developing countries from a predominantly lower tract site towards the upper tract.

In various studies from other countries, a positive family history of renal stone was reported in 11% to 21% of children. In our series, 26 % of children had a positive family history. This stresses the need for screening of family members especially sibling screening, in patients with renal stones, to diagnose stones at an early stage, thereby preventing the progression to renal failure.

The mean stone size of girls in our study population was 9.27mm and in boys it was 8.73mm. The p value of the test comparing the relation of stone size to gender was 0.77, which is greater than 0.05 showing statistically insignificant relationship between gender and stone size.

24 hour urinary estimation of various metabolic parameters is, to date, the gold standard test for the metabolic evaluation of stone disease. Various levels of evidence propose that hypercalciuria is directly implicated in stone formation. The frequency of hypercalciuria in our study was 34 %. This is in close agreement to the result obtained by Akhil joshi et al., from India who studied 39 subjects with urolithiasis and reported the frequency of hypercalciuria in their population to be 41%. Ismail Dursen et al., from Turkey reported the incidence of hypercalciuria to be 42.3%. However Mitra Naseri et al., from Iran and N.S. Hussain from Malaysia reported the incidence of hypercalciuria in their study to be 17 % and 14.6 % respectively. They attributed the low consumption of milk and milk products, low sodium intake or excessive sodium loss

through sweating as hot climate as possible causes for lesser incidence of hypercalciuria in their population.

Urinary excretion of oxalate is an important factor determining the formation of urinary calculi. In our study 52 % of the children showed hyperoxaluria. This is similar to the result obtained from studies by NS Hussain et al from Malaysia and Akhil Joshi et al from India who showed the incidence of hyperoxaluria to be 61% and 56 % respectively. However, Mitra Naseri et al from Iran showed that the frequency of hyperoxaluria in their study was 11%. The higher incidence of hyperoxaluria in our population (52 %) may be due to genetic factors or high dietary oxalate intake or low calcium intake. Absence of colonization of the gut with Oxalobacter formigenes could also be a factor responsible for this high prevalence of hyperoxaluria in our children. Considering the significant family history associated with hyperoxaluria, genetic factors seem to be an important determinant responsible for the higher incidence of hyperoxaluria.

There are controversial data about the excretion of urinary citrate in stone formers. Deficiency of citrate which is an inhibitor of stone formation is an important factor causing stone formation. Hypocitraturia is found in 14% of our study population. However, from the study in north india by Akhil Joshi et al., and Kumar et al., it was concluded that hypocitraturia is the single most important contributor to stone formation. Kumar et al., also found that the value of citrate in urine of recurrent stone formers were much less when compared to first time stone formers. Nevertheless, the value of hypocitraturia in different studies are highly varying with a study from Iran reporting a frequency of 2.1% and at the other end of the spectrum, study from India by Akhil Joshi reporting the incidence of hypocitraturia to be 82%.

In 34% of the children mixed abnormalities were found. 10% of children had more than 2 metabolic abnormalities in urine. 2 children had hypercalciuria and hypocitraturia, with ultrasound finding of nephrocalcinosis, with normal anion gap metabolic acidosis. The children were diagnosed to have distal renal tubular acidosis.

The finding of metabolic abnormality helps us to give a more specified treatment for the patients. Since there is a possibility of recurrence even after the surgical removal of stone, metabolic evaluation should be done for all patients, without which the treatment is incomplete.

CONCLUSION

24 hour urine metabolic workup is the gold standard in metabolic evaluation of patients with urolithiasis. Whenever a stone is discovered, a thorough search must be undertaken in the hope of uncovering a specific metabolic cause. Hyperoxaluria followed by hypercalciuria was the most common metabolic abnormality detected in our pediatric population. Anatomic abnormality was detected in 6 % of children in our study group. Only 6% of children had no metabolic abnormality, underscoring the need for 24 hour urinary metabolic work up in all children with urolithiasis. An increasing number of children with stone disease undergo surgical treatment following which they think that the problem is over. They are not aware of the chances of recurrence and possibility of progression to end stage renal disease. Stress must be laid to explain to the parents the importance of metabolic work-up of stone disease and that recurrence and ESRD could be avoided by appropriately treating the metabolic abnormality, only then will they adhere to the medical treatment and dietary advice properly.

LIMITATIONS OF OUR STUDY :

- Our Institute being a high volume tertiary care pediatric center, we were able to include sufficient number of urolithiasis cases in our study, though the incidence of urolithiasis in pediatric population is rare. However, this study is only a single-center study. A multi-center study would minimize selection bias.
- We have not included a control group in our study.

RECOMMENDATIONS :

1. 24 hour urine metabolic work-up should be done in all patients with urinary tract calculi.
2. Screening of family members has to be done, whenever possible.
3. Medical treatment appropriately suited for the child must be started even after the surgical removal of stone in order to prevent recurrence.

Thus it must clearly be borne in mind that a stone in the urinary tract is mostly a sequelae to underlying metabolic or anatomic abnormality, and hence the cause for it should be aggressively looked for.

ABBREVIATIONS

d- RTA	Distal renal tubular acidosis
ARF	Acute renal failure
SIADH	Syndrome of inappropriate anti diuretic hormone secretion
IEM	Inborn error of metabolism
GSD	Glycogen storage disease
PUV	Posterior urethral valves
IBD	Inflammatory bowel disease
CT	Computerized tomography
MAG 3	Mercapto-Acetyl-triGlycine
ESWL	Extra corporeal shock wave lithotripsy
PCNL	Per cutaneous nephrolithotomy

URS	Ureteroscopic removal of stones
RIRS	Retrograde intrarenal surgery
UTI	Urinary tract infection
BMI	Body mass index
ICD	International classification of diseases
USG	Ultrasonography
KUB	Kidney-ureter-bladder
SPSS	Statistical Package for the Social Sciences
SD	Standard deviation
SE	Standard error
E.coli	Escherichia coli
ESRD	End stage renal disease

PATIENT DATA FORM

STUDY TOPIC: METABOLIC EVALUATION IN RENAL STONE FORMERS

Name : Age & sex :

IP No : RC No :

Address : Religion :

History

Abdominal pain	Y	N
Gross hematuria	Y	N
Nausea and vomiting	Y	N
Fever	Y	N
Flank pain	Y	N
Abnormal urine colour	Y	N
Dysuria/cry during micturition	Y	N

Dribbling and difficult voiding	Y	N
Frequency of micturition	Y	N
Growth retardation	Y	N
Urinary retention	Y	N
Diagnosed by ultrasonography for different reasons	Y	N
Diagnosed by microscopic hematuria or crystal in urine	Y	N
Family h/o renal stones	Y	N
Previous h/o similar complaints	Y	N
H/O intake of drugs like frusemide,antacids, vit D, vit C	Y	N
H/O surgical intervention for the stone	Y	N

Dietary history

Investigations

- Ultrasonography of abdomen
- Xray abdomen
- CT abdomen

S.urea	S.creatinine	S.sodium	S.potassium	S.bicarbonate

S.Calcium	S.Phosphorus	S.Magnesium	S.Alkaline Phosphatase	S.Uric acid

- PTH,25 OH vit D(as and when needed)
- Urine routine

Albumin	**Sugar**	**Deposits**	**pH**

24 hour urinary	**Patient's value**	**Normal value**
Calcium		
Citrate		
Uric acid		
Oxalate		

Random urine	**Patient's value**	**Normal value**
calcium/creatinine		
citrate/creatinine		
uric acid/creatinine		
oxalate/creatinine		

- urine sodium nitroprusside test(cystine)
- Arterial blood gas analysis and acid load test (as and when needed)

DIAGNOSIS :

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Master Chart

S.No.	name	age in years	sex (1=male ,2=female)	rc no	abd pain (1= yes,0=no)	dysuria (1= yes,0=no)	Family h/o renal stones (1= yes,0=no)	hematuria (1= yes,0=no)	vomiting (1= yes,0=no)	fever (1= yes,0=no)	flank pain (1= yes,0=no)	abnormal urine colour (1=	dribbling (1= yes,0=no)	frequency of micturition (1=	growth retardation (1= yes,0=no)	urinary retention (1= yes,0=no)	diagnosed by imaging for	diagnosed by microscopic	previous h/o similar complaint	h/o intake of drugs like frusemide	usg (single=1,multiple=0)
1	ramya	0.66	0	568/09	0	1	1	1	1	1	0	0	0	0	0	1	0	1	0	0	0
2	priya	9	0	201/13	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	n
3	anusuya	9	0	198/13	1	1	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1
4	tejo vikram	1	1	780/14	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	pavithra	2	0	123/13	0	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	1
6	shabana	12	0	789/14	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1
7	deiva priya	4	0	313/12	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
8	akilesh	2.5	1	521/14	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	1
9	poojitha	2.5	0	444/14	0	1	0	1	0	0	1	0	0	0	0	0	0	1	0	0	1
10	Keerthivasan	8	1	827/13	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
11	Sherwin	1.5	0	458/13	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
12	Balachandar	0.66	1	554/12	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0
13	paun kumar	0.83	1	389/13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	Vikram	1	1	370/12	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	n
15	Vetrivel	5	1	674/12	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
16	Elakiyan	4	1	308/12	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
17	Rahul	10	1	641/12	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	Kanishka	4	0	302/13	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	n
19	Manikandan	4	1	495/11	0	0	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0
20	Deepika	5	0	243/13	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
21	Gokulprasad	0.92	1	274/13	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
22	Rithika	10	0	777/14	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1
23	Lokeshwaran	4	1	667/12	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
24	Edwin	5	1	804/11	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	n
25	Aswin	10	1	808/14	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
26	Hemanth	0.66	1	701/14	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	Dilliganesh	4	1	639/14	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
28	Raman	7	1	737/10	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0
29	Laxmanan	7	1	672/10	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0
30	Swetha	10	0	742/14	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
31	cheran	9	1	557/10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	Logeshkumar	0.75	1	514/13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
33	sabarigirinatha	1	1	013/12	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1
34	shiva	0.83	1	824/14	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	n
35	mohammed	2	1	7786188	0	0	0	1	0	1	1	1	0	0	0	0	0	0	0	0	1
36	swathi	9	0	533/14	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
37	jessica	4	0	148/14	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
38	deepak raj	10	1	164/14	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
39	suman kumar	6	1	60/14	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
40	purushothamn		1	453/14	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	sairam	7	1	207/12	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
42	Thyagarajan	12	1	652/14	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
43	thillaikarasu	8	1	526/14	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1
44	pavithra	9	0	95/14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	Kaviya	2	0	101/13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
46	gunasekar	12	1	569/14	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	Adarsh	1	1	790/14	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1
48	Madhavan	12	1	659/12	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
49	Jenifer	3	0	626/14	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	n
50	mano	3	1	788/14	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0

Master Chart

S.No.	usg(u/l right =1, u/l left=2,b/l	usg(renal =0,ureter =1,bladder =2)	usg-stone size	usg (hydronephrosis/hydrourete	usg (nephrocalcinosis present=1	Xray Abdomen	CT Abdomen	Bl.Urea	S.Creatinine	S.Sodium	S.Potassium	S.Bicarbonate	S.Calcium	S.Phosphorus	S.Magnesium	S.AlkalinePhosphatase	S.UricAcid	S.VitaminD	S.PTH	Ur.Alb	Ur.Sugar
1	0	0/1	3mm	0	0	-	normal	39	0.8	143	4	17	8.1	4	3	90	3.6	28.1	24.5	nil	nil
2	n	n	n	n	n	-	normal	15	0.8	145	3.9	20	8.8	4.1	1.8	180	4.2	23.5	15.1	nil	nil
3	1	1	5mm	0	0	-	normal	18	0.5	145	5.4	18	8.2	3.8	2.2	196	2.8	22	18	nil	nil
4	0	0	10mm	1	0	-	-	14	0.6	142	3.2	18	8.8	4.4	2.7	216	2.4	25	40	+	nil
5	1	0	6mm	0	0	-	-	28	1	138	4.4	18	9.2	3.8	3.1	280	6.2	26	24	nil	nil
6	1	0	7mm	0	0	-	r midport	25	0.8	134	4	18	9.5	6.3	1.9	178	4.1	30	34	nil	nil
7	0	0	7mm	0	0	-	-	20	0.5	148	2.9	18	7	4.2	2.4	240	3.2	18	33	nil	nil
8	1	0	5mm	0	0	-	-	17	0.6	135	3.8	21	10.2	5.5	2.3	230	3.5	20	54	nil	nil
9	1	0	6mm	0	0	-	-	19	0.5	139	4.1	20	10	4.5	1.9	170	3.1	16.2	34	1+	nil
10	0	0	7mm	0	0			20	1	140	3.8	18	9	4.4	1.7	166	5.1	15.7	23.3	nil	nil
11	0	0	31mm	0	0			36	0.8	142	3.8	12	10.6	6.8	2.4	233	4.1	23	24.4	1+	nil
12	0	0	5mm	0	0			36	0.5	144	3.2	18	11.8	7	2.6	245	5.3	24.4	5.2	nil	nil
13	1	0	6mm	0	0			18	0.5	137	3.9	19	9	4	3.1	98	3.3	25.4	11	nil	nil
14	n	n	n	1	0		7mm stone	22	0.8	140	3.5	22	8.7	4.3	2.8	105	3.6	28	18	2+	NIL
15	0	0	13mm	0	0			52	0.7	142	5.3	15	9.6	7.6	2.5	177	5.1	19.8	32	nil	nil
16	2	0	4mm	0	0			18	0.7	140	4.4	18	11.6	10.2	2	134	6	21.8	23	nil	nil
17	2	0	5mm	0	0			28	0.8	149	4.6	18	9.7	5.2	2.2	154	2.9	22.4	24	nil	nil
18	n	n	n	0	0		5mm rena	25	0.6	142	4.2	18	9.6	4.2	2.6	143	3.6	21.3	24.1	nil	nil
19	0	0	n	0	1			42	0.7	145	4.3	18	6.2	5.1	2.9	209	4.1	23.7	18.6	nil	nil
20	0	0/1	13mm	1	0			32	0.8	142	4.3	20	9.1	4.3	2.5	243	2.7	30	23.3	nil	nil
21	0	0	4mm	0	0		normal	26	0.6	141	4	16	10.2	4.6	2.7	222	3.6	36.2	24.3	3+	nil
22	1	0	8mm	0	0			28	0.7	134	4.5	21	9	6.6	2.1	234	0.8	33	22.6	nil	nil
23	0	0	19mm	0	0			26	0.7	146	3.8	20	9.3	4.2	2.7	210	2	32	18.9	2+	nil
24	n	n	n	n	n		normal	35	0.8	134	4.2	21	9.2	5.1	3.1	240	1.6	21	16.4	nil	nil
25	1	0	6mm	0	0			21	0.8	138	4.1	22	9.8	4.1	3.3	180	2.1	17	19.5	nil	nil
26	0	0	6mm	0	0			28	0.8	134	4.5	24	9.2	4.1	2.8	166	3.1	13	24.4	nil	nil
27	n	1	8mm	0	0			32	1.1	141	4.2	19	7.8	4.2	2.9	156	4	17	33.4	nil	nil
28	0	0/2	22mm	1	0			18	0.7	138	3.5	20	9.1	4.2	1.6	236	6.1	19.8	32.4	nil	nil
29	2	0/2	13mm	1	0			25	0.8	140	4	22	9	3.7	1.9	243	5.1	25.4	35.6	nil	nil
30	1	0	16mm	1	0			22	0.8	140	4.1	19	9.2	4.2	1.7	222	3.8	23.6	32.1	nil	nil
31	0	0	n	0	1			21	0.5	135	3.6	16	11	4.3	1.8	214	3.6	20	44	nil	nil
32	1	1	12mm	1	0			24	0.7	134.3	4.3	22	9.3	4.7	2.4	132	4.1	23.6	32.7	nil	nil
33	2	0	13mm	1	0			25	1	142	4	21	9.6	4.6	2.2	134	3.4	30.5	32	nil	nil
34	n	n	n	0	0	normal	normal	22	0.6	137	3.8	17	8.2	5.8	2.6	230	3.5	18.3	22.3	nil	nil
35	0	0/1	18mm	0	0			14	0.7	130	4.2	19	8.7	7.3	1.7	113	12.5/3.3	19.3	45	3+	nil
36	n	2	6mm	0	0			27	0.7	140	3.6	17	8.1	4.2	1.5	119	4.2	22.2	41	nil	nil
37	1	0	8mm	0	0			20	0.9	143	3.5	19	9.2	4.1	2.4	120	4	16.4	28.2	nil	nil
38	0	0	5mm	0	0			22	0.7	135	40	21	9.8	4.8	2.2	140	6.4	32	22.3	nil	nil
39	1	0	11mm		0			20	0.5	142	3.1	20	8.8	4.2	3	134	5.1	22.4	18.4	nil	nil
40	0	0	n	0	1			19	0.7	129	5.4	17	10.1	5.2	3.1	220	4.2	22	79.9	nil	nil
41	0	0	n	0	1			38	0.8	144	3.4	17	9.5	2.5	3	268	4	18	20.1	nil	nil
42	2	0	8mm	0	0			19	0.5	137	4.2	18	7.8	4.6	1.6	134	2.5	24.3	17.9	nil	nil
43	1	0	5mm	0	0			24	0.6	138	4.4	17	8.2	4.1	1.9	180	5.1	30.4	23.6	nil	nil
44	0	0	6mm	0	0			24	0.6	139	3.7	23	9.1	4.2	2.2	200	3.6	26.5	18.6	nil	nil
45	2	0	5mm	1	0			25	0.6	132	3.7	22	9.8	6.1	2	176	2.8	19.9	27.3	nil	nil
46	1	0	6mm	0	0			22	0.8	134	4	19	8.8	4.2	2.5	160	5.1	25.6	17.6	nil	nil
47	0	0	6mm	0	0			29	0.8	141	4.5	18	8.6	5.2	2.5	145	2.6	24.6	21	nil	nil
48	2	0	6mm	0	0			20.4	0.9	137	4.3	19	8.5	4.8	2.2	234	3.5	28.9	23.4	nil	nil
49	n	2	12mm	0	0	stone+		18	0.8	138	3.5	21	9.1	4.1	2	180	3.6	30.4	34	nil	nil
50	2	0	4mm	0	0			18	0.7	135	3.9	19	8.3	3.9	3.1	144	5.3	10.4	45.4	nil	nil

Master Chart

S.No.	Ur.Deposits	Ur.pH	urine c&s	24hrs Ur.Calcium	24 hour ur calcium in	24hrs Ur.Citrate	24 HR UR Citrate mg/kg/da	24hrs Ur.UricAcid	24 hr uric acid in mg/kg/day	24hrs Ur.Oxalate	24 hr ur oxalate in mg/kg/day	Ur.SodiumNitroPrusside	ABG	diagnosis(hyperoxaluria=1,hypercalciuria=2,hyperuricosuria=3,hypocitraturia=4,hypercalciuria/h	weight (IN kg)	
1	nil	5.9	n	5	0.765	35.1	5.4	80.2	12.3	20	3.07	N		8	6.5	
2	nil	6	n	66.7	1.33	219	4.38	477	9.54	62.9	1.2	N		1	50	
3	calcium ox	5.2	n	207	5.1	288	7.2	376	9.4	30.5	0.7	N		2	40	
4	7-8 pus cel	6.3	n	0.92	0.1	45.35	5	63	7	8.7	0.9	N		1	9	
5	oxalate sto	7.1	n	43.2	3.6	64.8	5.4	93.6	7.8	11.6	0.97	N		1	12	
6	nil	6.4	n	122	6.7	108	6	113	6.2	9	0.5	N		2	18	
7	nil	6.1	n	62.7	5.7	60.5	5.5	184	16.7	4.4	0.4	N		8	11	
8	nil	5.2	n	64	5.5	52.6	4.5	246	21.39	9	0.76	N		3	11.7	
9	8 -10 pus c	5.4	n	38	3.8	45	4.5	96	9.6	15.8	1.6	N		1	10	
10	nil	4.9	n	75	3.7	300	15	285	14.2	6	0.3	N		3	20	
11	5-8 pus cel	6.7	n	44	4.4	45	4.5	122	12.2	6	0.6	N		3	10	
12	Ca,Uricac	7.1	n	0.26	0.05	35	7	45	9	1.9	0.3	N		9	5	
13	Plenty of C	5.8	n	20	2.8	11	1.5	49	7	2.3	0.32	N		4	7	
14	4-6 pus cel	5.4	n	22	2.4	27	3	81	9	11	1.2	N		1	9	
15	nil	6.5	n	16	0.8	131.4	7.3	316.5	17.5	23.6	1.3	N		6	18	
16	nil	6.4	n	9.3	0.6	91.5	6.1	96	6.4	30	2	N		1	15	
17	4-5 pus cel	4.7	n	85	3.5	124.8	5.2	283	11.7	27.5	1.1	N		6	24	
18	nil	7.1	n	11	0.8	53.3	4.1	4	0.3	14.9	1.1	N		1	13	
19	nil	6	n	77	5.5	81.2	5.8	88.2	6.3	7	0.5	N		2	14	
20	nil	5.9	n	16.7	0.8	0.8	0.04	136.8	7.2	10.9	0.5	N		4	19	
21	10-12 pus c	6	n	13.64	1.7	141.9	17.6	160.6	20	19.8	2.4	N		6	8	
22	nil	8.4	n	76	3.8	323	16.1	513.35	25.6	43.7	2.1	N		6	20	
23	5-10 pus ce	7	n	79	6	106.6	8.2	213	16.3	47	3.6	N		7	13	
24	calcium ox	5.8	n	82	4.1	330	16.6	417.8	20.8	22.3	1.1	N		7	20	
25	3-4 pus cel	6.4	n	80.8	3.2	105	4.2	265.4	10.6	17.1	0.6	N		3	25	
26	nil	6.7	n	30.8	4.4	52.3	7.4	45.5	6.5	7.2	1	N		5	7	
27	nil	5.5	n	30.1	2.3	87.5	6.7	231	7	10.5	0.8	N		1	13	
28	5-10 pus ce	8	n	21.1	1.1	73.8	4.1	99	5.5	73.3	4	N		1	18	
29	4-5 pus cel	5	n	30	1.6	75.6	4.2	111.6	6.2	112	6.3	N		1	18	
30	nil	6.5	n	119.16	3.6	92.4	2.8	210.48	6.3	28	0.8	N		1	33	
31	nil	7.7	n	5.8	0.2	84	4.2	182	9.1	21.2	1.1	N	normal anio	1	20	
32	nil	6.5	n	30.4	3.8	41.6	5.2	73.6	9.2	4.56	0.57	N		PUV/normal	8	
33	nil	4.9	proteus	36	3.6	40	4	91	9.1	6	0.6	N		PUV/normal	10	
34	nil	5	n	161	6.44			191.7	7.6	18.8	0.75	N		5	25	
35	3-4 pus cel	6	n	13.7	1	86.8	6.2	144	11	5.6	0.4	N		3	14	
36	nil	7.2	n	104	6.1	69.7	4.1	156.4	9.2	46.9	2.7	N		5	17	
37	nil	6.1	e.coli	68	4.5	90	6	149.9	9.9	16	1.06	N		5	15	
38	nil	5.5	n	69.6	1.9	94.5	2.7	304.8	8.7	24.2	0.68	n		9	35	
39	nil	6.4	n	88.1	5.18	98.6	5.8	344	20	44	2.6	n		7	17	
40	nil	6	n	8	2.6	27.6	9.2	27.3	9.1	1.8	0.6	n	-	1	3	
41	nil	8	n	55	5.5	13	1.3	90	9	5	0.5	N	normal anio	4	10	
42	nil	6.7	n	110	4.4	95	3.8	167.5	6.7	50	0.5	N		2	25	
43	nil	6	n	74.4	3.1	120	5	196.8	8.2	12	0.5	N		horse shoe kidney/normal	24	
44	nil	5.7		68	3.4	32	1.6	154	7.7	8	0.4	n		4	20	
45	nil	6.5	n	64.4	4.6	61.6	4.4	145.6	10.4	10.92	0.78	N		7	14	
46	nil	5	n	66	2.2	126	4.2	234	7.8	17.1	0.57	N		4	30	
47	nil	6	n	38.7	4.3	29.7	3.3	93.6	10.4	7.2	0.8	N		7	9	
48	nil	4.5	n	78	2.6	132	4.4	231	7.7	12	0.4	N		9	30	
49	3-4 pus cel	5.5	n	49	4.9	40	4	116	11.6	6	0.6	N		5	10	
50	nil	5.7	n	12.3	0.97	130	10.83	80.3	6.7	7.1	0.6	N		9	12	